TRALOMETHRIN

RISK CHARACTERIZATION DOCUMENT

Volume 1

HEALTH ASSESSMENT SECTION

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I. SUMMARY

A. INTRODUCTION

This document characterizes the potential risk associated with occupational, home use, and dietary exposure to the pesticide tralomethrin. This assessment was performed under the provisions of Senate Bill 950 (the California Birth Defect Prevention Act), and the Assembly Bill 2161 (sometimes referred to as the Food Safety Act). Senate Bill 950 requires a scientific determination that use of a registered pesticide will not cause significant adverse health effects. Assembly Bill 2161 requires risk assessments on the dietary exposure to pesticides in both raw and processed foods.

Tralomethrin is the common name for (1R,3S)3[(1'RS)(1',2',2',2',-tetrabromoethyl)]-2,2-dimethylcyclopropanecarboxylic acid (S)-alpha-cyano-3-phenoxybenzyl ester. This insecticide is a synthetic pyrethroid. The exact mode of action for tralomethrin is currently not known. It is generally assumed that pyrethroids affect neuroactivity by delaying the closing of sodium channels (Corbett et. al, 1984). This affects action potentials and often results in repetitive activity or blockage of nerve conduction.

Nine product formulations containing tralomethrin as the active ingredient have been submitted to the Department of Pesticide Regulation (DPR) for registration in California. Two of these products (Scout X-TRA™, and SAGA® WP) are marketed by Hoechst Roussel. The remaining 7 formulations (Hot Shot® Rid a Bug® Flea & Tick Killer, Hot Shot ® Rid a Bug® Home Insect Killer, Hot Shot® Roach and Ant Killer 2, Hot Shot® Roach and Ant Killer 3, Hot Shot® Triple Strength Roach and Ant Killer, Spectracide® Flea and Tick Killer 2, Spectracide® Home Insect Control 3) are marketed by Spectrum Group, United Industries Corporation.

Scout X-TRA™ is intended for use on cotton to combat a variety of insects. SAGA® WP is intended for use by professional applicators in and around residential and nonresidential structures and their immediate surroundings and on transportation vehicles (e.g., railroad cars). The remaining "Hot Shot®" and "Spectracide®" products are ready-to-use, "do-it-yourself" products.

The metabolism of tralomethrin has been extensively studied. This pesticide is generally not detected in treated animals or their excreta since it undergoes rapid and essentially complete debromination to form deltamethrin. Subsequent molecular cleavage gives rise to decamethrin and phenoxybenzoic acid.

B. TOXICOLOGY

A DPR review of the toxicology studies on the effects of tralomethrin has identified adverse responses. Laboratory animal studies have demonstrated toxicity in response to both acute repeated exposures to tralomethrin. The primary acute signs of toxicity are characteristic of cholinergic toxicity (i.e., indicators of autonomic nervous system dysfunction). This is consistent with the neurotoxicity associated with synthetic pyrethroids.

Specific clinical signs reported following acute exposure studies included: ptosis, labored respiration, excessive salivation, vomiting, diarrhea/liquid feces, locomotion difficulties, sedation, convulsions, tremors, and death. On the basis of the dose-related increase in autonomic nervous system dysfunction (liquid feces), an acute LOEL of 0.1 mg/kg/day was established for tralomethrin. An estimated NOEL of 0.01 mg/kg/day was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10. This value will be used in calculating margins of safety for acute exposure to tralomethrin.

The sub-chronic toxicity of tralomethrin was investigated in rats, mice, and dogs. As with acute studies, the primary toxic effects reported were characteristic of cholinergic toxicity. Sub-chronic effects reported in laboratory studies included: reduced liver weights, vomiting, liquid feces, clonic convulsions, unsteady gate, tremors, exaggerated patellar reflexes, and mortality.

A 90-day oral toxicity study with CD rats established a NOEL of 1 mg/kg/day. This was based on mortality observed at dosages of 6 mg/kg/day or greater. In CD-1 mice, a NOEL of 10 mg/kg/day was established on the basis of mortality, clonic convulsions, and unsteady gait reported at dosages of 15 mg/kg/day or greater. In the 13-week dog study, a sub-chronic LOEL of 0.1 mg/kg/day was established on the basis of exaggerated patellar reflexes, liquid feces and vomiting. An estimated sub-chronic NOEL of 0.01 mg/kg/day was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10.

The toxicity potential for chronic tralomethrin exposure has been established in mice, rats, and dogs. On the basis of dermatitis reported at oral doses of 0.75 mg/kg/day and greater in mice, the chronic LOEL established in this risk assessment was 0.75 mg/kg/day. No evidence of oncogenicity potential has been associated with tralomethrin exposure. An estimated chronic NOEL of 0.075 mg/kg/day was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10.

Tralomethrin was tested for genotoxic potential both *in vitro* and *in vivo*. Assays included the *Salmonella* gene mutation assay (Ames test), the host mediated assay, the L5178Y mouse lymphoma assay, tests for *in vitro* and *in vivo* chromosomal aberrations, a mouse dominant lethal assay, tests for DNA damage, and tests for morphological cell transformation. Genotoxic potential was indicated in the L5178Y mouse lymphoma assay in the presence of metabolic activation. In all other systems examined, no genotoxic potential was reported.

While no chemically related "reproductive effects" were reported in the reproductive studies evaluated, developmental effects were noted. A developmental NOEL of 3 mg/kg/day was established on the basis of decreased pup weight and increased neonatal mortality at 12 mg/kg/day. A NOEL of 0.75 mg/kg/day was established for weanlings on the basis of convulsions and death at 3 mg/kg/day.

In a study designed to evaluate the developmental effects of tralomethrin in New Zealand White rabbits, abortions were reported, at 25 mg/kg/day (Schardein, 1989). On the basis of this adverse effect, the developmental toxicity was established at 12.5 mg/kg/day.

C. EXPOSURE

Occupational exposure to tralomethrin has been evaluated by the Worker Health and Safety branch of DPR. Tralomethrin uses included treatment of cotton (Scout X-TRA™), professional pest control (SAGA®WP), and ready-to-use, do-it-your-self pest control (Hot

Shot® and Spectracide® products). Dosages were estimated for single day (Absorbed Daily Dosage, ADD), seasonal (Seasonal Average Daily Dosage, SADD), annual (Annual Average Daily Dosage, AADD) and lifetime (Lifetime Average Daily Dosage, LADD) exposures to agriculture workers involved in the treatment of cotton. The acute absorbed daily dosage was presented as both a mean and upper bound exposure estimate. This risk assessment assumes that an individual is unlikely to receive the maximum single day exposure every day of a repeated exposure scenario; therefore, the daily dosage estimates for seasonal, annual, and lifetime exposures are presented only as mean values. In addition to occupationally related exposures, this risk assessment considered exposures to professional applicators and residents from home use products and dietary exposure to commodities (e.g., cotton and soybean) treated with tralomethrin.

D. RISK CHARACTERIZATION

On the basis of the indicated adverse effects and estimated dosages, margins of safety were calculated for both occupational, residential, and dietary exposures to tralomethrin.

In general, a margin of safety equal to or greater than 10 is considered protective of human health when it is based on NOELs from human studies. When exposure is based on NOELs from non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100).

Estimated margins of safety, based on average acute exposure estimates and NOELs based on autonomic dysfunction (diarrhea/liquid feces), were greater than 100 for activities involved in ground boom application, and home applicators. All other activities had margins of safety less than 100. When tralomethrin exposure was based on the estimated upper bound (mean ± 2SD, or maximum value from range), all margins of safety were less than 100, with the exception of mixer/loaders involved in the ground boom application of the pesticide.

Calculated margins of safety based on seasonal exposures were less than 100 for cotton scouts, as well as, mixer/loaders, applicators, and flaggers involved in the aerial application of tralomethrin to cotton. All activities related to ground boom application to cotton were greater than 100.

Seasonal margins of safety were not calculated for residential PCO or home-owner applications since these applications are not seasonal.

On the basis of annual exposure estimates, calculated margins of safety for all agricultural and residential activities were greater than 100. Margins of safety for potential lifetime exposures were also greater than 100.

Margins of safety for potential acute dietary exposure to tralomethrin were calculated by taking the ratio of the experimentally determined NOEL to the potential dietary dosage. Margins of safety were less than 100 for infants and children ages 1 to 6. For all other population sub-groups, margins of safety were greater than 100.

Margins of safety for annual dietary exposures were greater than 100 for all population sub-groups.

When dietary exposure was combined with added to professional and home use exposures, the calculated margins of safety were similar to the values excluding dietary (i.e., dietary exposure from residues is a minor component of the total potential dosage). With the exception of applicators and mixer/loader/applicators involved in ground boom applications to cotton, all margins of safety that were greater than 100 in the absence of dietary exposure, were greater than 100 when the dietary component was added.

II. INTRODUCTION

This document characterizes the potential risk associated with dietary and occupational exposures to the pesticide tralomethrin. This assessment was performed under the provisions of Senate Bill 950 (California Birth Defect Prevention Act), and Assembly Bill 2161 (sometimes referred to as the Food Safety Act). Senate Bill 950 requires a scientific determination that use of a registered pesticide will not cause significant adverse health effects. AB-2161 requires risk assessments on the dietary exposure to pesticides in both raw and processed foods. Tralomethrin has been associated with cholinergic poisoning in laboratory animals and in humans (accidental poisoning and suicide attempts).

A. CHEMICAL IDENTIFICATION

Tralomethrin is the common name for (1R,3S)3[(1'RS)(1',2',2',2',-tetrabromoethyl)]-2,2-dimethylcyclopropanecarboxylic acid (S)-alpha-cyano-3-phenoxybenzyl ester. This insecticide is a synthetic pyrethroid. The exact mode of action for tralomethrin is currently not known. It is generally assumed that pyrethroids affect neuroactivity by delaying the closing of sodium channels (Corbett et. al, 1984). This affects action potentials and often results in repetitive activity or blockage of nerve conduction.

B. REGULATORY HISTORY

No tralomethrin products are currently registered in California. On September 18, 1985, a tolerance of 0.2 ppm (parts per million) for the combined residues of tralomethrin and its primary metabolites was established by the U.S. EPA for the raw agricultural commodity, cottonseed (U.S. EPA, 1985). On June 17, 1987, a tolerance of 0.05 ppm for the combined residues of tralomethrin and its metabolites calculated as parent in or on the raw agricultural commodity soybeans was established. On June 29, 1988, and amended June 30, 1989 a tolerance of 0.20 ppm was established for the combined residues of tralomethrin and its metabolites in or on cottonseed oil, when present as a result of application of the insecticide to the growing crops.

C. TECHNICAL AND PRODUCT FORMULATIONS

Nine product formulations containing tralomethrin as the active ingredient have been submitted to DPR for registration in California. Two of these products (Scout X-TRA™, and SAGA® WP) are marketed by Hoechst Roussel. The remaining 7 formulations (Hot Shot® Rid a Bug® Flea & Tick Killer, Hot Shot® Rid a Bug® Home Insect Killer, Hot Shot ® Roach and Ant Killer 2, Hot Shot® Roach and Ant Killer 3, Hot Shot® Triple Strength Roach and Ant Killer, Spectracide® Flea and Tick Killer 2, Spectracide® Home Insect Control 3) are marketed by Spectrum Group, United Industries Corporation. The nine products, with U.S. EPA registration numbers and the percent active ingredient, are presented in TABLE I.

TABLE I: Tralomethrin products.

Product Name	**% Active Ingredient**
Scout X-TRA™ (EPA Reg No. 34147-3-54382)	11.40
SAGA® WP (EPA Reg No. 432-755)	40.00
Hot Shot® Rid a Bug® Flea & Tick Killer (9688-81-8845)	0.025
Hot Shot® Rid a Bug® Home Insect Killer (EPA Reg No. 9688-80-8845)	0.01
Hot Shot® Roach and Ant Killer 2* (9688-86-8845)	0.01
Hot Shot® Roach and Ant Killer 3 (EPA Reg No. 9688-80-8845)	0.01
Hot Shot® Triple Strength Roach and Ant Killer* (EPA Reg No. 9688-79-8845)	0.03
Spectracide® Flea and Tick Killer 2 (EPA Reg No. 9688-87-8845)	0.03
Spectracide® Home Insect Control 3 (EPA Reg No. 9688-81-8845)	0.025

D. USAGE

Scout X-TRA™ is sold as a liquid that contains 11.4% tralomethrin. It is intended for use on cotton to combat a variety of insects. This product is a Toxicity Category I pesticide that has the signal word "DANGER" on the label. The application rates for use on cotton range from 0.016 to 0.024 pounds active ingredient (ai) per acre (2.28 to 3.41 fluid ounces per acre). The first application is to be made "before insect populations are significant." Subsequent applications can be made as needed. The total number of applications to cotton crops in a single growing season is restricted to 10. Scout X-TRA™ may be applied in tank mixtures with other products approved for use on cotton. This includes applications of the following synthetic pyrethroids: AMBUSH®, AMMO® 2.5EC, ASANA® XL, BATHROID® 2, CAPTURE® 2EC, CYMBUSH®, DANITOL® 2.4 EC, FURY™ 1.5EC, KARATE®, MUSTANG®, POUNCE® 2.3EC, and Scout X-TRA™. Scout X-TRA™ may be applied by aerial or ground application. The total amount of Scout X-TRA™ that may be applied to cotton in a single growing season is 0.19 pounds ai per acre (27 fluid ounces per acre). Scout X-TRA™ may not be applied within 28 days of harvest for cotton. Applicators and other handlers must wear long-sleeved shirt and long pants; chemical-resistant gloves; shoes plus socks; and protective eyewear. Worker reentry into treated areas is prohibited for 24 hours after treatment. In the event that early reentry is required, workers must wear coveralls, chemical-resistant gloves, shoes plus socks, and protective eyewear.

SAGA® WP is a wettable powder containing 40% active ingredient. This product is intended for use by professional applicators in and around residential and nonresidential structures and their immediate surroundings and on transportation vehicles (e.g., railroad cars). SAGA® WP is intended to be mixed with water and applied with hand pressurized or power operated sprayers as a course spray. The application concentrations of tralomethrin may vary from 0.03 to 0.06% w/w (0.1 to 0.2 ounce SAGA® WP). Treatments may be repeated as necessary to maintain adequate pest control. This product is a Toxicity Category II pesticide with the signal word "WARNING".

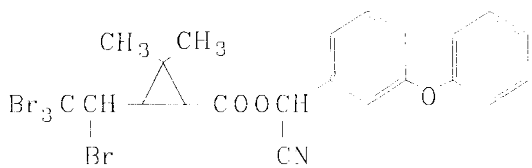
The remaining "Hot Shot®" and "Spectracide®" products are ready-to-use, "do-it-yourself", water based formulations with 0.1 to 0.3 % active ingredient (see TABLE I). These products are Toxicity Category III pesticides that carry the signal word "CAUTION".

E. ILLNESS REPORTS

Since tralomethrin has not been registered in California, there is no record of human illnesses. The toxicity of deltamethrin (the primary tralomethrin metabolite) to humans has, however, been documented (Note: While deltamethrin is registered by the U.S. EPA, it is not currently registered by California.). He et al., (1989) have reported 325 cases of deltamethrin poisonings due to agricultural use and accidental or suicidal poisoning. Oral ingestion has been associated with epigastric pain, nausea, vomiting, coarse muscular fasciculation, and coma. Workers exposed to deltamethrin during its manufacture experienced cutaneous and mucous membrane irritation.

F. PHYSICAL AND CHEMICAL PROPERTIES[1]

1. Chemical Name: ((S-alpha-cyano-3-phenoxybenzyl (1R,3S)-2,2-dimethyl-3-[(RS)-1,2,2,2-tetrabromoethyl]-cyclopropanecarboxylate
2. Common Name: Tralomethrin
3. Trade Names: Scout X-TRA®; Tracker®; Saga®; Dethmor®; Chemsico® Home Insect Control; Hot Shot Rid-a-Bug®; Spectracide™
4. Structural Formula:



5. Empirical Formula: $C_{22}H_{19}Br_4NO_3$
6. CAS Registry Number: 66841-25-6
7. Molecular Weight: 665
8. Specific Gravity: 0.948g per ml at 20°C (Scout)
1.032g per ml at 20°C (Technical)
9. Physical State: Yellow to beige resin (Technical)
9. Boiling Point: Not applicable
10. Solubility: Soluble in most organic solvents, but relatively insoluble in water (i.e., 0.026 ppm in 30 minutes, 0.036 ppm in 24 hours)
11. Vapor Pressure: 4.6×10^{-13} mmHg at 25°C
12. Octanol/Water Partition Coefficient: 3.5×10^{4} at 25°C
13. Henry's Law Constant: 5.04×10^{-12} atm/m^3 per mole
14. pH: 6.8 (in a 1% aqueous dispersion)

[1](Hoechst-Roussel, 1987,1988a-d)

G. ENVIRONMENTAL FATE

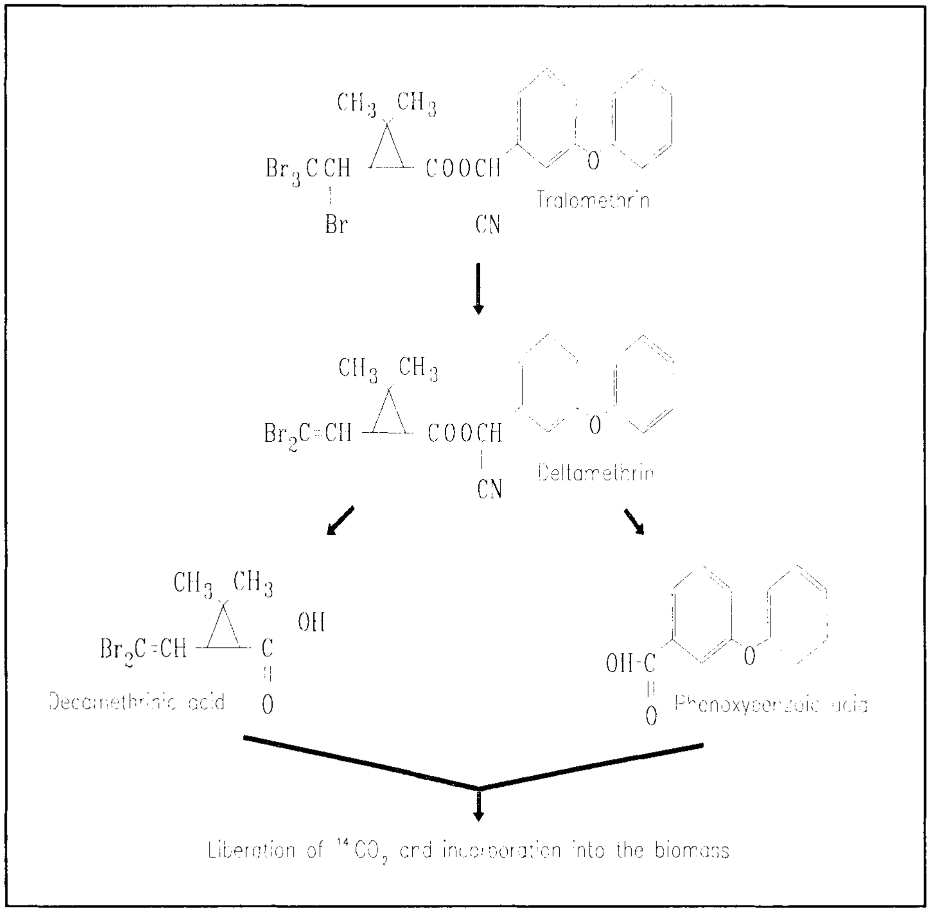
SUMMARY

The environmental fate studies evaluated in this risk assessment indicate that tralomethrin is unstable under both aerobic and anaerobic conditions. The parent compound rapidly undergoes debromination to form deltamethrin. The half-life of tralomethrin is approximately 3 days (aerobic conditions). Subsequent molecular cleavage gives rise to decamethrin and phenoxybenzoic acid. The calculated half-life of deltamethrin is approximately 33 days (aerobic conditions). The major degradation products are the same after hydrolysis, aqueous photolysis, soil photolysis, and plant metabolism. Studies indicate that due to soil adsorption properties, tralomethrin has a low potential for ground water contamination. A study with bluegill sunfish indicated that tralomethrin can bio-accumulate. Furthermore, the physical and chemical properties (e.g., low water solubility, high octanol/water partition coefficient, and low vapor pressure) are characteristic of a chemical that would be relatively immobile in soil, have a low potential to leach, and a high potential to bio-accumulate (Ney, 1990).

1. Aerobic Metabolism

The aerobic soil metabolism of tralomethrin was investigated by Wang (1990a). Under aerobic conditions in a sandy loam soil, with an application rate of 0.2 ppm, tralomethrin rapidly underwent debromination to form deltamethrin. Subsequent molecular cleavage gave rise to decamethrin and phenoxybenzoic acid. These two metabolites were then mineralized to carbon dioxide and incorporated into the soil biomass (see Figure 1 for a graphic representation).

Figure 1: Tralomethrin: Proposed Metabolic Pathway in Sandy Loam Soil Under Aerobic Conditions



The reported half-life for the parent compound was approximately 3 days. The formation and decline of deltamethrin appeared to reach equilibrium by 7 days post-application. The calculated average half-life for deltamethrin was 33 days

2. Anaerobic Metabolism

The metabolism of tralomethrin under anaerobic conditions was investigated by Wang (1990b). Under laboratory conditions at 25°C in the dark, tralomethrin was allowed to degrade aerobically for 3 days (approximately one half-life under aerobic conditions). This was followed by 91 days of anaerobic conditions induced by flooding with degassed deionized water. As with the aerobic study discussed above, an application rate of 0.2 ppm in sandy loam soil was used. Tralomethrin rapidly underwent debromination to form deltamethrin. Final anaerobic metabolites were essentially the same as reported for aerobic metabolism.

After 30 days of flooding, no tralomethrin was detected. At the 30 day time period, deltamethrin accounted for 35% to 40% of the applied chemical. After 91 days deltamethrin accounted for 11% to 13%. Br_2CA increased steadily until reaching approximately 60% by day 91. Phenoxybenzoic acid increased to approximately

21% during the first 60 days of flooding. It then declined to approximately 3% by day 91.

3. Hydrolysis

The hydrolytic behavior of tralomethrin at pH 4, 5, 7, and 9 was examined by Wang (1990c). The test was conducted in the dark at 25°C. Initial debromination of the parent compound to form deltamethrin was detected at all pH levels. The calculated half-lives of tralomethrin were 95, 940, 33, and 37 days at pH 4, 5, 7, and 9, respectively (Note: the value at pH 5 [940] is assumed to be a report typographical error and should be 94) The major degradation products were the same as those reported in the soil metabolism studies.

4. Aqueous Photolysis

The photodegradation of tralomethrin in a pH 5 aqueous solution under simulated sunlight was examined by Wang (1991d). The irradiation was conducted at 25°C with intermittent 12 hour light and dark cycles each day for 30 days. Samples were harvested at 0, 2, 3, 7, 14, 21, and 30 days post treatment. The calculated half-life for tralomethrin under test conditions was 3.6 days. The major degradation products were the same as those reported in the soil metabolism studies.

5. Soil Photolysis

The photodegradation of tralomethrin in sandy loam soil, under simulated sunlight was examined by Wang (1991e). The irradiation was conducted at 26°C with intermittent 12 hour light and dark cycles each day for 30 days. The calculated half-life for tralomethrin under test conditions was 6.4 days. The major degradation products were the same as those reported in the soil metabolism studies. The calculated half-life for combined pyrethroids under test conditions was 18 days.

6. Leaching Potential

A soil adsorption/desorption study was conducted at 25°C, in the dark, with radio-labeled tralomethrin and four soil types (i.e., sand, sandy loam, loam, and clay loam). Tralomethrin was found to be immobile in all four soil types. Quantitative interpretation of the study was hindered, however, by excessive sorption of the test material to the test containers. The study director did, however, indicate that the study implied that tralomethrin would adsorb to soil rather than remain in solution.

7. Plant Residues/Metabolism

The metabolism of tralomethrin in plants has been investigated (Hoechst-Roussel, 1985). The isomeric mixture of tralomethrin and its individual isomers was reported to dissipate from cotton leaves with half-lives of 10 days. Tralomethrin was debrominated to deltamethrin. The half-life of deltamethrin was also reported to be 10 days. The degradation of deltamethrin produced decamethrinic acid and phenoxybenzoic acid (see animal metabolism).

8. Fish Accumulation

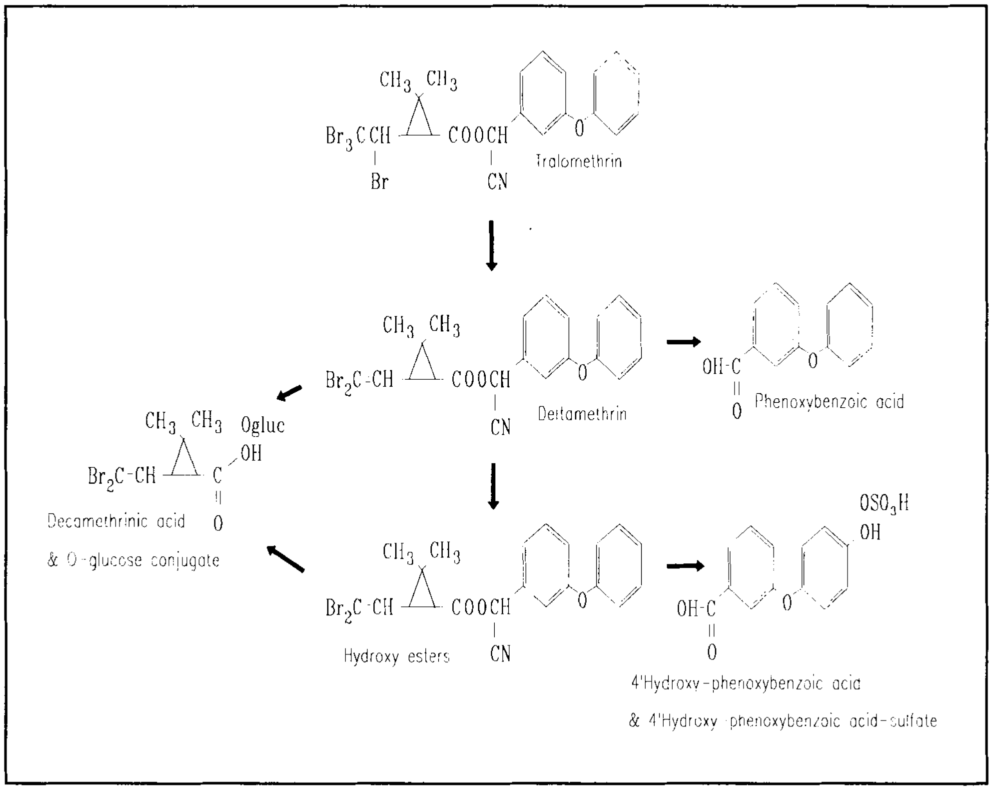
The uptake, depuration, and bioconcentration, by fish, of radio-labeled tralomethrin was investigated by Thompson (1983). In this study, bluegill sunfish were exposed to 0.085 µg/l ^{14}C-tralomethrin for 30 days (groups of 100 fish each were placed in duplicate and control test chambers). Water and fish were observed every 24 hours during the uptake (exposure) period. Following the 30 day exposure period, water in the test chambers was replace with well water and the fish were held in this "depuration phase for 21 days. Radio-analysis of whole fish, fillet, and viscera was conducted at various times throughout the uptake and depuration phases of the study. A gradual uptake of ^{14}C-tralomethrin was reported. Daily bioconcentration factors ranged from 180-490, 47-100, and 310-920 for whole fish, fillet and viscera, respectively. Uptake tissue concentration ranges were 13-36 ppb, 3.5-10 ppb, and 23-68 ppb for whole fish, fillet and viscera. Accumulation was reported to reach a steady-state plateau after 14 of exposure. During this depuration period, radio-analysis indicated 89, 79, and 88 percent clearance rates for whole fish, fillet, and viscera, respectively. Utilizing linear regression analysis, an uptake rate constant of 58 ppb in whole fish, per ppb in water, per day was calculated. A steady-state bioconcentration factor of 530 was calculated.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS/METABOLISM

The metabolism of tralomethrin by the rat has been extensively studied by Cole, et al. (1982) and Bosch (1990). Tralomethrin is generally not detected in treated animals or their excreta since it undergoes rapid and essentially complete debromination to form deltamethrin (Figure 2).

Figure 2: Tralomethrin: Proposed Metabolic Pathway in Rats.



Deltamethrin is then hydroxylated at the 2', 4', and 5' positions of the alcohol moiety and the methyl group trans to the carboxylate linkage. Ester cleavage reactions and further metabolism yields alcohols, carboxylic acids and their glucuronide, glycine, and sulfate conjugates. Based on cumulative recovery profiles (Bosch, 1990), the majority of the radioactivity (from ^{14}C labeled tralomethrin) was eliminated from the (in the urine and feces) rat within the first 24 hours after dosing. Radioactivity retained in tissues and carcasses 7 days post treatment ranged from 0.5% to 1.5% of the administered dosages.

A dermal absorption study of tralomethrin in male rats was conducted by Hazleton Laboratories and reported by Thongsinthusak (1995). The study utilized six week old male Sprague-Dawley rats (Charles River Crl:CD®BR). One day prior to the exposure, the backs and shoulders of each rat were shaved and the shaved areas were washed with acetone. A plastic enclosure was affixed to the shaved area to define the treated area (approximately 12.5 cm^2). An Elizabethan collar was placed on the animal's neck to prevent it from licking the treated skin site. Three dose levels and one control were used in this study. The final doses were 0.037, 0.378, and 1.18 mg/animal (equivalent to 3, 30, and 95 $\mu g/cm^2$) After administration of the test material, the treated skin site was covered with a non-occlusive cover made with filter paper. The sacrifice times for the definitive phase of the study were: 0.5, 1, 2, 4, 10, 24, and 120 hours. For the 24- and 120-hour sacrifice times, treated skin sites were washed with soap solution (ten hours after exposure). Daily urine and feces samples were collected and analyzed separately. Samples collected for analysis were: non-occlusive covers, dose enclosures, skin washings, treated skin sites, cage washings, cage wipes, carcasses, feces, and urine. The results indicated that dermal absorption of tralomethrin is not directly proportional to dose (TABLE I). Furthermore, the percentage of tralomethrin absorbed is directly related to exposure time. A low percent of dose (range 0.07-0.78) was observed in carcasses for all dose groups and sacrifice times. The highest percent of dose which remained in the skin was 24.3% at 10-hour sacrifice time for the low dose; whereas, for medium and high doses the residues were 6.71 and 4.97% at 10-hours after dosing, respectively.

Excretion kinetics of tralomethrin in urine and feces from treated rats were observed for 120 hours after dosing. The maximum cumulative percent absorbed (including amounts found in urine, feces, and that bound to skin [defined as the asymptote]) was estimated by employing an exponential saturation model with a lag time. The dermal absorption value is the sum of percent dose at the asymptote and percent of dose recovered in carcass, blood, and cage washings/cage wipes. The percent of dose in the blood in the present study was considered negligible. The adjusted dermal absorption values for the lowest dose (3 $\mu g/cm^2$) of 7.2% is appropriate to use in the exposure estimates because this dose should be representative of exposure experienced by agricultural workers or consumers.

TABLE I. Summary of tralomethrin dermal absorption values for low, medium and high doses (from Thongsinthusak, 1995).

		Percent of dose					Adjusted*
Dose ($\mu g/cm^2$)		CW/CW	Carcass	Excretion at Asymptote	Total	% Recovery	% Dermal Absorption
Low	3	1.74	0.37	4.66	6.77	94.6	7.2
Medium	30	1.09	0.31	1.82	3.22	99.8	3.2
High	95	0.56	0.36	1.89	2.81	97.7	2.9

CW/CW = Cage wash/Cage wipe

* Adjusted for percent recovery

B. ACUTE TOXICITY

SUMMARY

Laboratory animal studies have demonstrated toxicity in response to acute exposure to tralomethrin. The primary toxic signs are characteristic of cholinergic poisoning. This is consistent with the neurotoxicity associated with synthetic pyrethroids. Specific clinical signs reported in acute toxicity (LD_{50}) studies included: ptosis, labored respiration, locomotion difficulties, sedation, convulsions, tremors, and death.

The acute toxicity profile for tralomethrin (technical) and Scout X-TRA (a product containing approximately 10% tralomethrin) is summarized in TABLES II and III. The technical material is approximately 3 times more toxic than the 10% product in the rat when given by oral gavage. Neither the technical material nor the 10% product were lethal up to 2,000 mg/kg in the rabbit dermal studies. In rabbit eye irritation studies, the 10% product was classified as a Category I while the technical material was identified as a toxicity Category II.

TABLE II: Tralomethrin: Acute toxicity of technical grade material.

Tralomethrin (technical)	
Oral LD_{50} (rat)	85 mg/kg (in Polyethylene glycol)[a]
Oral LD_{50} (rat)	99 mg/kg (in Sesame oil)[a]
Dermal LD_{50} (rabbit)	>2,000 mg/kg (in Sesame oil)[b]
Dermal Irritation (rabbit)	Category IV (in Sesame oil)[c]
Eye Irritation (rabbit)	Category II (in Sesame oil)[d]
Inhalation LC_{50} (rat)	>0.286 mg/L[e]

a, Glomot, 1979a; b, Glomot, 1979b; c, Glomot, 1979c; d, Glomot, 1979d; e, Jackson et al., 1980.

TABLE III: Tralomethrin: Acute toxicity of Scout X-TRA, a 10% active ingredient formulation.

Scout X-TRA Insecticide (~10% Tralomethrin)

Oral LD_{50} (rat)	284 mg/kg[a]
Dermal LD_{50} (rabbit)	>2,000 mg/kg[b]
Dermal Irritation (rabbit)	Category II[c]
Dermal Sensitization (Guinea Pig)	Negative[d]
Eye irritation (rabbit)	Category I[e]
Inhalation LC_{50} (rat)	1.4 mg/L[f]

a, Myer, 1987a; b, Myer, 1987b; c, Myer, 1987c; d, Myer, 1987d; e, Myer, 1987e;f, Ulrich, 1989

C. SUB-CHRONIC TOXICITY

SUMMARY

The sub-chronic toxicity of tralomethrin was investigated in rats, mice, and dogs. As with the previously discussed acute studies, the primary toxic effects are characteristic of cholinergic poisoning. Cholinergic signs were reported in all three species. On the basis of the data reviewed, dogs were the most sensitive to the toxic effects of tralomethrin while mice were the least sensitive. The spectrum of reported effects included: reduced liver weights, vomiting, liquid feces, clonic convulsions, unsteady gate, tremors, exaggerated patellar reflexes, and mortality.

1. Oral Study (Rat)

Tralomethrin was administered by gavage to Charles River CD® rats for 13 weeks (Laveglia, 1980a). Treatment dosages included 0, 1, 6, and 18 mg/kg/day. Twenty male and female animals were treated for each dose group. Decreased activity and motor control were reported during the first week of the study in the high dose group. Soft stool, and labored breathing (usually noted prior to death) were also reported for animals at dosage group. Thirty-two (17 females and 15 males) of the 40 animals in the 18 mg/kg/day group and 1 female animal in the 6 mg/kg/day group died or were killed during the first week of the study. These effects were not reported in animals in subsequent weeks. A statistically significant ($p<0.05$) decrease in mean organ weight (absolute and relative) was reported for the male livers at the mid and high dose and in the female at the all treated doses. On the basis of animal mortality at 6 and 18 mg/kg/day, the NOEL for this study was 1 mg/kg/day. The Department of Pesticide Regulation of the California

Environmental Protection Agency (DPR) considered this study acceptable as a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guideline study.

2. Oral Study (Mice)

An 8-week oral gavage study was conducted with Charles River CD-1 mice (Laveglia, 1980b). This study was performed as a range-finder to establish doses for a mouse oncogenicity study. Tralomethrin was administered, by gavage, to mice at dosage levels of 0, 5, 10, 15, 20, and 30 mg/kg/day. Each group consisted of 10 male and 10 female mice. The major signs reported are presented in TABLE IV.

TABLE IV: Tralomethrin: Clinical signs reported (percentage of animals) in 8-week oral gavage study was conducted with Charles River CD-1 mice (Laveglia, 1980b).

Percentage of Mice with Signs[1]						
Signs	**Dosage Level (mg/kg/day)**					
	0	**5**	**10**	**15**	**20**	**30**
Excessive Salivation	0	0	15	90	90	60
Unsteady Gait	0	0	5	80	80	0
Clonic Convulsions	0	0	0	25	85	95
Death	0	0	0	20	70	100

[1] Ten male and ten female animals per dose.

Increases in yellow staining on the anogential area, excessive salivation, and unsteady were reported at doses of 10 mg/kg/day and greater. This effects were dose-related from 10 to 15 mg/kg/day, then leveled off or began to drop off at lethal dosages (20 and 30 mg/kg/day). Clonic convulsions and death occurred in a dose-related fashion at 15, 20 and 30 mg/kg/day. At 15 mg/kg/day, 4 animals died (3 males and 1 female). The males died during the first, third and sixth weeks, while the female died during the 3rd week. At 20 mg/kg/day, 11 animals (4 males and 7 females) died during the first week. Three additional animals (all males) died in subsequent weeks (2 in the second week, and 1 during the third week. All animals in the 30 mg/kg/day group died during the first week of the study.

The NOEL for this study was 5 mg/kg/day based on unsteady gait and excessive salivation. DPR considered this study supplemental to the tralomethrin data base.

3. Oral Study (Dogs)

Forty beagles (5 males and 5 females per dose group) were used to study the subchronic effects of tralomethrin (Chesterman, et al., 1978). Exposures were by gelatin capsule, once a day, and included a vehicle control (polyethylene glycol), 0.1, 1.0, and 10.0 mg/kg/day tralomethrin. The duration of dosing was for 13 weeks followed by a 6-week observation period (2 males and 2 females per dose group). The clinical signs included; refusal of milk supplement, vomiting, liquid feces, exaggerated patellar response, and tremors. The primary effects are presented in TABLE V .

TABLE V: Tralomethrin: Clinical signs reported in 13-week oral toxicity study conducted in beagles (Chesterman, et al., 1978).

Clinical Signs (reported cases)[1,2]

Signs	Dosage Level (mg/kg/day)			
	Control	0.1	1.0	10.0
Vomiting				
Week 1	0	0	2	17
Weeks 1-13	1	2	9	40
Liquid Feces				
Week 1	1	7	11	17
Weeks 1-13	17	52	84	246
Tremors/Uncoordination				
Week 1	0	0	0	8
Weeks 1-13	0	0	0	155
Exaggerated Patellar Reflex				
Week 4	0	1	2	6
Weeks 6	0	2	19	56

1 Clinical signs were not recorded on days 3, 4, 5, and 6.

2 Five males and five females for each dose group

During the first week of dosing, refusal of milk supplement and tremors were reported only at the high dose (10 mg/kg/day), while dose-related increases in vomiting was reported at 1 and 10 mg/kg/day. A dose-related increase in liquid feces was reported in all dose groups. Since these effects were observed during the first week of dosing, they were assumed to be in response to acute exposure. Furthermore, these indicators of autonomic nervous system dysfunction (vomiting, liquid feces, and tremors) were observed within 1-7 hours of dosing. The actual incidence rates for the first week may be underestimates as clinical signs were not recorded on days 3, 4, 5, or 6.

Throughout the study (i.e., weeks 1 through 13), the frequency of the reported signs increased. Unsteadiness, body tremors, and uncoordinated movements were reported in the high dose group. A dose related increase in milk supplement refusal was reported at, 1, and 10 mg/kg/day. Dose related increases in vomiting and liquid feces were reported at all doses. Furthermore, these increases did not appear to be related to gender.

Exaggerated patellar reflexes were observed in the high dose group (10 mg/kg/day) from the second week on. During the fourth and sixth weeks, all treatment groups exhibited exaggerated patella reflexes in a dose related fashion.

No biologically significant histopathological variations were attributed to tralomethrin exposure in the trachea, lungs, liver, kidney, or nervous system.

On the basis of the exaggerated patellar reflexes, vomiting, and liquid feces reported in the Chesterman et al., (1978) study, the LOEL for the sub-chronic effects of tralomethrin is 0.1 mg/kg/day. On the basis of signs of autonomic nervous system dysfunction (liquid feces) reported to have occurred during the first week of dosing, the LOEL for the acute effects of tralomethrin from this study was 0.1 mg/kg/day. To illustrate the continuum of effects associated with acute exposure to tralomethrin, this study established an acute NOEL of 1 mg/kg/day on the basis of tremor induction at 10 mg/kg/day. It should be noted that while this information was considered in the risk assessment process, due to a lack of dosage quantification (the purity of the test article was not disclosed, the dose preparation was not described, the stability of the dosing solutions was not given, and the analysis of dosing solutions was not reported), the Chesterman et al., (1978) report was considered unacceptable, but possibly upgradable, to DPR as a FIFRA guideline study.

TABLE VI summarizes the effects reported in the tralomethrin sub-chronic studies. As indicated, a 90-day oral toxicity study with CD rats established a NOEL of 1 mg/kg/day. This was based on mortality observed at dosages of 6 mg/kg/day or greater. In CD-1 mice, a NOEL of 10 mg/kg/day was established on the bases of deaths, clonic convulsions, and unsteady gait reported at dosages of 15 mg/kg/day or greater. In the dog study, a sub-chronic LOEL of 0.1 mg/kg/day was established on the basis of exaggerated patellar reflexes, liquid feces and vomiting.

TABLE VI: Tralomethrin: Sub-Chronic Toxicity

Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects
Oral Toxicity (Rat)[1]	1.0	6.0	mortality
Oral Toxicity (Mouse)[2]	5.0	10.0	unsteady gait and excessive salivation
Oral Toxicity (Dog)[3]	<0.1	0.1	exaggerated patellar reflexes, liquid feces, and vomiting

1 Laveglia, 1980a
2 Laveglia, 1980b
3 Chesterman, et al., 1978

D. CHRONIC TOXICITY AND ONCOGENICITY

Summary

The toxic and/or oncogenic potential associated with chronic exposure to tralomethrin was evaluated in dietary studies with rats and mice, and an oral study with dogs. As with the previously discussed acute and sub-chronic studies, the primary toxic effects were classic signs of autonomic nervous system dysfunction (i.e., characteristic of cholinergic toxicity). Cholinergic signs were reported in all three species. On the basis of the data reviewed, mice were the most sensitive to the toxic effects of tralomethrin while rats were the least sensitive. The range of reported effects included: reduced liver weights, vomiting, liquid feces, clonic convulsions, unsteady gate, tremors, exaggerated patellar reflexes, and mortality. Abnormal movements were associated with tralomethrin exposure in all three species. No oncogenic potential was reported.

1. Combined Toxicity/Oncogenicity Study (Rat)

Tralomethrin was administered, by gavage, to male and female CD rats, for 24 months, at 0, 0.19, 0.75, or 3.0 mg/ml (Spicer, 1984). Administration was in corn oil at a volume of 4 ml/kg. Dosages were, therefore, 0, 0.75, 3.0, and 12 mg/kg/day. Eighty animals per dose, per sex, were used for tralomethrin groups. Two control groups (1 with 80 animals per sex and 1 with 60 animals per sex) were examined. Animals in the high dose group exhibited excessive salivation which started 3-4 hours after dosing. This effect was observed throughout the study. High dose animals also exhibited uncoordinated movements, and an inability to support weight on limbs. These signs were observed after 40 weeks for males and after 53 weeks for females. A significant decrease in body weight gain was reported for males in the high dose group. When compared to controls, the group mean body weight in high these animals was approximately 22% less than the control values (655g vs. 831g and 847g for control groups). For high dose females, the difference was approximately 8% (452g vs. 484 and 497 for control groups). No treatment-related effects were reported in hematologic parameters, biochemistry, urinalysis, organ weights, or tumor induction. The systemic NOEL for this study was 3 mg/kg/day based on the reported clinical signs related to nervous system toxicity at 12 mg/kg/day. DPR considered this study acceptable as a FIFRA guideline study.

2. Oral Oncogenicity Study (CD-1 Mouse)

The potential oncogenic effects of tralomethrin were investigated in a 2 year study with Charles River CD-1 mice (Spicer, 1983a). Tralomethrin was administered, by gavage, to male and female mice, at 0, 0.75, 3.0, or 10 mg/ml. Administration was in corn oil at final dosages of 0, 0.75, 3.0, and 10 mg/kg/day. Eighty animals per dose, per sex, were used for tralomethrin groups. Two control groups (1 with 80 animals per sex and 1 with 60 animals per sex) were examined. Clinical observations in the high dose animals included a decrease in survival (27% vs. 55% in the control animals), excessive salivation (observed between 45 minutes and 3 hours after dosing [reported throughout the study]), uncoordinated involuntary movements (primarily during the first 18 months of the study), and aggressiveness (after week 4). As indicated in Figure 3, statistically significant ($p<0.05$) increases in the incidence of dermatitis was reported in tralomethrin treated males (5/80, 7/37, 8/39, 12/29 for 0, 0.75, 3.0, and 10 mg/kg/day, respectively [reported throughout the study]).

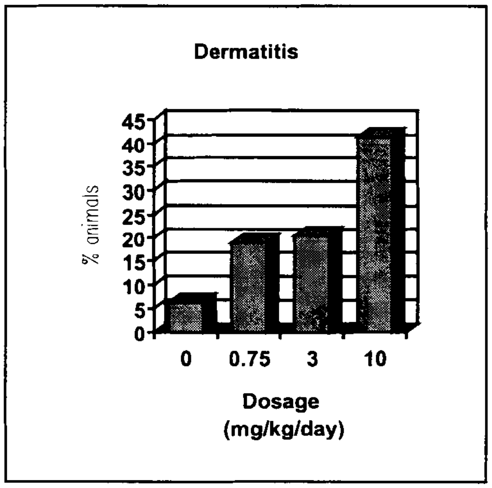


Figure 3: Percent of animals with dermatitis reported in a 2-year mouse study (Spicer, 1983a).

No significant changes in hematological or biochemical results were reported. Other than dermatitis related signs, no significant test article related signs were reported. The LOEL for systemic toxicity was 0.75 mg/kg/day, based on the significant incidence of dermatitis at all doses. No significant changes in the incidence of tumors between treated and control animals were reported. DPR considered this study acceptable as a FIFRA guideline study.

3. Oral Toxicity Study (Dog)

A 1-year study was conducted to examine the effects of tralomethrin on dogs (Spicer, 1980). The test article was administered to purebred beagles (8 males and 8 females per treatment group), orally by capsule, at dosages of 0, 0.75, 3.0, and 10.0 mg/kg/day. Due to body trembling, ataxia, prostration, and convulsions, the 10 mg/kg/day dosage level was decreased to 8 mg/kg/day on study week 4, and to 6 mg/kg/day on study week 14. On the fourth week of the study, the 0.75 mg/kg/day dosage level was increased to 1.0 mg/kg/day. Signs reported in the study are indicated in TABLE VII.

TABLE VII: Tralomethrin: Clinical signs reported (% of animals affected) in 1-year oral toxicity study conducted in beagles (Spicer, 1980).

Signs	**Dosage Level (mg/kg/day)**			
	Control	**0.75**	**3.0**	**10.0**
Diarrhea				
Weeks 1-13	100	100	100	100
Weeks 14-26	100	100	100	100
Weeks 27-39	75	100	100	100
Weeks 40-52	83	100	92	100
Vomiting				
Weeks 1-13	50	81	100	100
Weeks 14-26	75	69	94	100
Weeks 27-39	75	42	92	91
Weeks 40-52	75	75	100	100
Tremors				
Weeks 1-13	0	6	19	100
Weeks 14-26	0	0	0	93
Weeks 27-39	0	0	8	64
Weeks 40-52	0	0	0	73
Convulsions				
Weeks 1-13	0	6	0	63
Weeks 14-26	0	0	0	13
Weeks 27-39	0	0	0	0
Weeks 40-52	0	0	0	9
Ataxia				
Weeks 1-13	0	0	0	100
Weeks 14-26	0	0	0	100
Weeks 27-39	0	0	8	100
Weeks 40-52	0	0	0	91

1 Eight male and 8 female animals were treated for each dose group. One female in the high dose group died during week 3 of the study. Two animals from each group were killed after 26 weeks.

Diarrhea (liquid feces), a sign that was reported to be dose-related in the sub-chronic dog study (Chesterman, et al., 1978), occurred in most animals in the chronic study (exceptions were control animals from weeks 27-52 and 3 mg/kg/day animals from weeks 40 to 52 [see TABLE VII]). While the Chesterman study reported weekly responses, the current study presents responses for 13-week periods. Due to high background levels during the first 13 weeks of the present study and the different reporting methods, a direct comparison of cases of diarrhea in the two studies is not possible. Vomiting and ptyslism (excessive salivation) were also reported throughout the study in both treated and controls. Both appeared to be dose related during the first 13 weeks of the study. Throughout the 52-week study, however, vomiting appeared to be dose related at all doses while ptyslism showed increases at the top two doses (vomiting data shown in TABLE VII and Figure 4). This data is consistent with the dose-related increase reported in the sub-chronic study (Chesterman study).

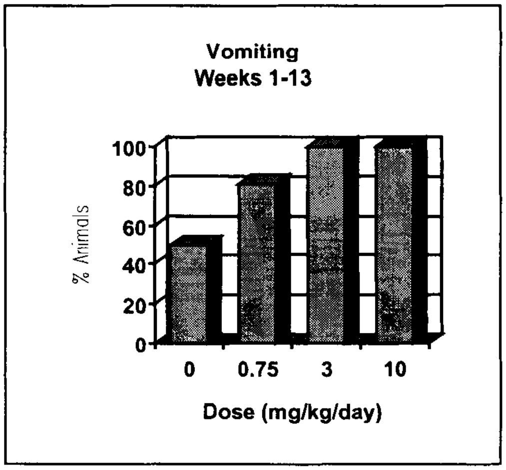


Figure 4: Percent of animals reported to have vomiting episodes during the first 13-weeks of a 1 year toxicity study in dogs (Spicer, 1980). Tralomethrin was administered in corn oil to groups of 8 animals/sex/dose.

In addition to the previously described effects, at the high dose, tremors, convulsions, and ataxia were observed throughout the study, with the exception that no convulsions were reported weeks 27 through 39 (TABLE VII). Tremors and ataxia were reported at 3 mg/kg/day. Nineteen percent of the animals (2 males and 1 female) exhibited tremors during the first 13 weeks, while 8 percent (1 female) exhibited tremors and ataxia from week 27 to 39. Tremors and convulsions were reported in one female dog at 0.75 mg/kg/day during week 13 of the study. These signs were not, however, used in determining a chronic NOEL since no tremors or convulsions were reported in any animals, at 0.75 mg/kg/day, from week 14 to the end of the study. No toxicologically significant changes were reported for hematology, biochemistry, body and organ weights, necropsy, or histopathology.

On the basis of ataxia, and tremors, DPR considered the chronic NOEL for the toxic effects of tralomethrin on dogs to be 0.75 mg/kg/day. DPR considered this study acceptable as a FIFRA guideline study.

TABLE VIII summarizes the results of the chronic toxicity and/or oncogenicity studies conducted with tralomethrin. As indicated, a 24 month oral study with CD rats established a NOEL of 3 mg/kg/day. This was based on excessive salivation, uncoordinated movements, inability to support weight on limbs, and decrease in body weight gain at 12 mg/kg/day. In CD-1 mice, a LOEL of 0.75 mg/kg/day was established on the bases of dermatitis. In the dog study, a NOEL of 0.75 mg/kg/day was established on the basis of tremors and ataxia in animals exposed to 3 mg/kg/day tralomethrin. Tremors and convulsions were reported in one animal at 0.75 mg/kg/day. These signs were not, however, used in determining a chronic NOEL since no tremors or convulsions were reported in any animals, at 0.75 mg/kg/day, from week 14 to the end of the study.

TABLE VIII: Tralomethrin: Chronic Toxicity

Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects
Combined Oral Toxicity/ Oncogenicity (rat)[1]	3.0	12.0	excessive salivation, uncoordinated movement, inability to support weight on limbs, and decrease in body weight gain.
Oral Oncogenicity (Mouse)[2]	<0.75	0.75	dermatitis.
Oral Toxicity (Dog)[3]	0.75	3.0	tremors and ataxia[a]

[1] Spicer, 1984
[2] Spicer, 1983a
[3] Spicer, 1980

E. GENOTOXICITY

Summary

Tralomethrin was tested for genotoxic potential both *in vitro* and *in vivo*. Assays included the *Salmonella* gene mutation assay (Ames test), the host mediated assay, the L5178Y mouse lymphoma assay, tests for *in vitro* and *in vivo* chromosomal aberrations, a mouse dominant lethal assay, tests for DNA damage, and tests for morphological cell transformation. Genotoxic potential was indicated in the L5178Y mouse lymphoma assay in the presence of metabolic activation. In all other systems examined, no genotoxic potential was reported.

1. Gene Mutation

a) Bacteria

Tralomethrin was tested for mutagenic potential in the *Salmonella typhimurium* gene mutation assay (Ames test) with tester strains TA98, TA100, TA1535, TA1537 and TA1538 (Vannier, et al., 1980). The test was conducted both in the presence and absence of a rat liver metabolic activation solution. Tralomethrin concentrations (in DMSO) included 0, 2, 10, 50, 200, 500, 1,000, and 5,000 µg/ml. No increase in the number of revertants, when treated values were compared to controls, was reported (i.e., tralomethrin was not mutagenic under the test conditions). DPR considered this study acceptable as a FIFRA guideline study.

b) Mammalian cells

The ability of tralomethrin to mutate mammalian cells was tested in the L5178Y mouse lymphoma gene mutation assay (Cifone, 1982). Based on toxicity limits, test article concentrations ranged from 0.02 to 3.9 µg/ml in the absence of metabolic activation and 1.9 to 40 µg/ml in the presence of a metabolic activation system (S-9 fraction of rat liver homogenate). No increase in mutant frequency was reported for the non-activated portion of the test. In the presence of a metabolic activation system, however, a significant, dose related increase in mutant frequency was observed. While genotoxic potential was indicated by this study, the results were not confirmed in an independent assay. DPR, therefore, considered the study unacceptable and not upgradeable as a FIFRA guideline study.

2. Structural Chromosomal Aberration

c) *In Vivo* cytogenetics

A metaphase analysis of rat chromosomes following exposure to tralomethrin was reported by Richold, et al. (1982). This study was designed to evaluate the cytogenetic potential of tralomethrin in the bone marrow of Sprague Dawley CD rats. For this study, rats were treated with 0, 30, 60, or 120 mg/kg tralomethrin. Administration was by intragastric intubation. At three different times after dosing (4, 22, and 46 hours) five males and five females from each dose group were administered chochicine by intraperitoneal injection. No treatment related increase in chromosomal aberrations was reported. DPR considered this study acceptable as a FIFRA guideline study.

An *in vivo* mouse micronucleus assay was performed to test the genotoxic potential of tralomethrin (Vannier, et al., 1980). Swiss CD1 mice were treated with 0, 6, 12, or 24 mg/kg tralomethrin by gavage. The vehicle and negative control was sesame oil. Each animal (5 per sex per dose group) was administered the total dosage in two equal treatments separated by 24 hours. No mortality was reported. No test article related increase in micronucleated polychromatic erythrocytes was reported. Interpretation of this study, however, was impaired by a number of deficiencies in the study and report. These deficiencies included, inadequate information on the test article, no justification for dose level selection, and an inadequate number of sampling times. DPR considered the study unacceptable and not upgradeable as a FIFRA guideline study.

d) *In Vitro* cytogenetics

An *in vitro* cytogenetic assay was conducted with tralomethrin and CHO cells by Putman (1988). The test article was tested in the presence and absence of an Aroclor-induced metabolic activation system (S-9). Doses in the absence of S-9 included 0.7, 1.3, 2.5, 5, and 10 µg/ml. Doses in the presence of S-9 were 7, 13, 25, and 50 µg/ml. Under the conditions of this test, tralomethrin did not induce an increase in chromosomal aberrations in CHO cells. DPR considered this study acceptable as a FIFRA guideline study.

The *in vitro* cytogenetic potential of tralomethrin was investigated by Galloway (1982). For this study, Chinese hamster ovary (CHO-WBI) cells were used as the test system. Cultures of these cells were exposed to the test article at doses ranging from 100 ng/ml to 333 µg/ml (in a half log series). Maximum doses were based on solubility in culture medium. The assay was conducted in the presence and absence of a metabolic activation system (rat liver S-9 mix). No test article related increases in chromosomal aberrations was reported. Study deficiencies, including an inadequate number of harvest times and an inadequate number of duplicates, rendered the study unacceptable and not upgradeable to DPR as a FIFRA guideline study.

e) Rat Dominant Lethal Assay

A dominant lethal assay was conducted with tralomethrin in Sprague-Dawley rats (Allen, 1982). In this assay, tralomethrin was administered by intragastric intubation to male rats at dosages of 0, 1, 4, or 12 mg/kg/day for 10 weeks. At the end of the treatment period, the males were paired (weekly) with groups of untreated females for 4 consecutive weeks. Pregnant females were killed on day 13 of gestation and their uterine contents examined. Clinical signs reported in the high dose group (12 mg/kg/day) included, unsteady gait, impaired use of hand legs, body tremors, hunched posture, and piloerection. Salivation after dosing was reported at all 3 treatment levels. At the terminal necropsy, no macroscopic changes that could be associated with treatment were reported. No treatment related effects were observed in male mating performance, the number of implantations, viable embryos, early and late embryonic deaths, or pre- and post-implantation losses. While no evidence of a relationship between tralomethrin and dominant lethal effects was indicated, this study was deficient in that no positive control was used and the dosing solutions were not analyzed. DPR considered the study unacceptable and not upgradeable as a FIFRA guideline study.

3. Other Genotoxic Effects

a) DNA Damage

The effects of tralomethrin exposure on unscheduled DNA synthesis (UDS) in rat hepatocytes was investigated by Curren (1988). The test material was tested in the UDS assay at seven dose levels ranging from 5 to 5,000 µg/ml. The study indicted that under the test conditions, tralomethrin did not cause a significant increase in the mean number of net nuclear grains when compared to control values. DPR considered this study acceptable as a FIFRA guideline study.

The effects of tralomethrin exposure on DNA damage and repair was investigated in *E. Coli* by Vannier, et al. (1980). This bacterial growth inhibition test, utilizing various *E. Coli* strains and DNA repair deficient mutants, did not indicate genotoxic potential. A number of deficiencies, however, were apparent. These deficiencies included, no indication of test article purity or stability indicated, individual data not reported, metabolic activation not included, no justification of dose selection. DPR considered the study unacceptable and not upgradeable as a FIFRA guideline study.

F. REPRODUCTIVE TOXICITY

Summary

Studies were conducted to monitor the effects of tralomethrin on rat reproduction. While no chemical related reproductive effects were noted, developmental effects were reported in both studies. These effects included decreased pup weight and neonatal mortality. Weanling toxicity was also demonstrated.

1. Oral Study (Rat)

A two-generation study was conducted to evaluate potential effects of tralomethrin on the reproductive performance of Charles River COBS CD rats (Spicer, 1983b). The test article was administered, by gavage in corn oil, at dose levels of 0.75, 3.0, and 12.0 mg/kg/day. The F_0 and F_1 generations involved 12 male and 24 female rats. Treatment was for a minimum of 100 and 120 days for F_0 and F_1 generations, respectively. Due to a low number of litters, the F_0 rats were re-mated to produce F_{1b} litters. Weanlings were selected from the F_{1b} litters and mated to produce F_2 animals. A decrease in mean body weight ($p<0.05$) was reported for males from the high dose F_0 group and the mid and high dose F_{1b} group. A reduction in pup weight was observed in the high dose group of the F_{1a}, F_{1b}, and F_2 generations. During the study, eight rats from the F_0 generation died. These included one control, three mid-dose, and four high dose animals. Two of the mid-dose and two of the high dose animals likely died due to intubation error, as indicated by esophagus damage observed in necropsy (i.e., unexplained deaths included 1 control and 1 high dose animal. One mid-dose and 13 high dose F_1 weanlings died shortly after initiation of dosing. Prior to death, convulsions were observed in all of these animals. No test article related macroscopic (based on post-mortem examination) or microscopic lesions (adrenals, colon, heart, ileum, jejunum, kidney, liver, lungs, ovary, spleen, stomach, testis, thyroid, urinary bladder, prostate, uterus, and cervix), nor organ weight changes were reported. The maternal NOEL for this study was 12 mg/kg/day (highest dose tested). The paternal NOEL for this study was 0.75 mg/kg/day, based on decreased body weight gain. The developmental NOEL was 3 mg/kg/day, based on decreased pup weight. A systemic (weanling) NOEL of 0.75 mg/kg/day was also determined, based on convulsions and deaths occurring in weanlings. DPR considered this study acceptable as a FIFRA guideline study.

Additional Reproduction Studies

A study was conducted to examine the effects of tralomethrin on neonatal growth in rats (Schardein, 1983). For this study, pregnant Charles River COBS CD rats were administered tralomethrin at dosage levels of 0, 0.5, 0.75, 3.0, or 12.0 mg/kg/day. Administration was by gavage beginning on gestation day 15 and continuing through day 20 of lactation. On lactation day 21, dams and pups were euthanized. Dams from the high dose group (12 mg/kg/day) exhibited reduced body weight gain (67% of control) during gestation days 15-20. Excessive salivation (3 of 20 animals) was also reported in this group. At 12 mg/kg/day, all pups in one litter were stillborn. In 3 additional litters, all pups were dead by day 4. The number of live pups at day 4, compared to day 0, was 79.9% for the high dose group and 97.5% in the controls. Furthermore, a significant decrease (86-90% of control, $p<0.05$) in mean pup body weight on lactation days 0 and 4 was reported for the high dose group. The maternal NOEL for this study was 3.0 mg/kg/day, based on reduced body weight gain. The developmental NOEL for this study was also 3.0 mg/kg/day. This was based on neonatal toxicity and decrease in pup body weight. DPR considered this study supplemental to the tralomethrin data base.

G. DEVELOPMENTAL TOXICITY

Summary

The toxicity of tralomethrin in developmental studies was investigated in Sprague Dawley CD1 rats and New Zealand White rabbits. In the rat study, maternal effects included piloerection and sedation. A statistically significant increase in post-implantation fetal losses was also reported. This effect, however, was not considered, by DPR, to be toxicologically significant. In the rabbit study, abortions were reported in high dose animals. DPR considered these effects to be related to maternal toxicity rather than developmental toxicity. No other treatment-related fetal effects were reported. Developmental effects were, however, reported in studies designed to investigate the reproductive effects of tralomethrin (see REPRODUCTIVE TOXICITY).

1. Gavage Study (Rat)

A study was conducted to investigate the potential of tralomethrin to induce embryotoxic or teratogenic effects in Sprague Dawley CD1 rats (Vannier and Glomot, 1980a). Pregnant rats were administered daily dosages of 0, 2, 6, or 18 mg/kg tralomethrin, by gavage, in corn oil. Twenty-five mated females were used for each exposure group. Dosing occurred on days 6 through 17 of gestation. One female in the 18 mg/kg group exhibited signs of reaction to the treatment (piloerection and sedation) on gestation day 22 then died on day 23. No treatment related effects were noted in body weight changes. The mean number of implantations and viable fetuses were reported to be consistent throughout the groups. A significant ($p<0.01$) increase in post-implantation losses was observed in all treated groups, when compared to concurrent controls (TABLE IX).

TABLE IX: Tralomethrin: Post implantation losses reported in a developmental study conducted in Sprague Dawley CD1 rats (Vannier and Glomot, 1980a).

	Dosage (mg/kg/day)			
	0	2	6	18
Fetal Losses	1/255	11/250	17/260	9/228
Percentages	0.4	4.4	6.5	4.0
Mean/Female	0.05	0.52	0.77	0.45

Differences between control and treated values were statistically significant ($p \leq 0.01$). In the absence of a clear dose-related increase, DPR did not consider the effect toxicologically significant. The maternal NOEL for this study was 6 mg/kg/day, based on piloerection, sedation, and death reported at 18 mg/kg/day. The developmental NOEL for this study was 18 mg/kg/day (highest dose tested). DPR considered this study acceptable as a FIFRA guideline study.

2. Gavage Studies (Rabbit)

The developmental toxicity and teratogenic potential of tralomethrin was investigated with rabbits (Schardein, 1989). Sixty-four inseminated New Zealand White SPF female rabbits were randomly assigned to one control and three treatment groups (16 animals per group). Tralomethrin dosages levels for the treatment groups included 6.25, 12.5, and 25 mg/kg/day (in corn oil). All animals were treated (by gavage) by a single daily dose on days 7 through 19 of gestation. On day 29 of gestation, cesarean sections were performed on all surviving females. One animal in the 25 mg/kg/day group died on day 26 of gestation. Prior to death, this animal aborted and the following signs were reported: reduced motor activity, labored breathing, and emaciation. Two other animals from this exposure group aborted, one on gestation day 23 and the other on gestation day 27. Other clinical signs reported in this study are presented in TABLE X.

TABLE X: Tralomethrin: Summary of maternal observations reported in a developmental study conducted in New Zealand White SPF rabbits (Schardein, 1989).

Maternal Observations Number of animals and percentages								
	Concentration (mg/kg/day)							
	0		6.25		12.5		25	
	#	%	#	%	#	%	#	%
No visible abnormalities	7	(44)	4	(25)	5	(31)	3	(19)
Reduced motor activity	0	(0)	0	(0)	0	(0)	1	(6)
Aborted	0	(0)	0	(0)	0	(0)	3	(19)
Died	1	(6)	0	(0)	0	(0)	1	(6)

Other than the indicated abortions, no fetal malformation or developmental variations were reported for any of the dose groups. The maternal NOEL for this study was 12.5 mg/kg/day, based on abortions and death (While abortions may be the result of maternal or fetal toxicity, the DPR data review considered the abortions maternal toxicity). The fetal NOEL for this study, therefore, was 25 mg/kg/day, the highest dose tested. DPR considered this study acceptable as a FIFRA guideline study.

Vannier and Glomot (1980b) reported on another study designed to investigate the embryotoxic and teratogenic potential of tralomethrin in rabbits. In this study New Zealand White rabbits were mated with proven males and placed into various dosage groups. The dosage levels of tralomethrin included; 0, 2, 8, and 32 mg/kg/day. Administration was oral by gavage on days 6 through 18 of gestation (15 females per dose group). No treatment related effects were reported; however, the study had a number of inadequacies. These included incomplete fetal examinations and inadequate justification for dose level selection. DPR considered this study unacceptable and not upgradeable as a FIFRA guideline study.

H. NEUROTOXICITY

The acute delayed neurotoxicity of tralomethrin to domestic hens was investigated by Roberts et al. (1980). The study was designed to establish the oral LD_{50} of tralomethrin to adult domestic hens and to determine the neurotoxic potential of the pesticide. The study was conducted in two parts. In the LD_{50} determination, six groups of 5 animals were given tralomethrin by gavage at 0, 1,000, 2,000, 3,000, 4,000, or 6,000 mg/kg. One mortality occurred in the 1,000 mg/kg group and two mortalities were reported in the 6,000 mg/kg group. In the neurotoxic portion of the study, six groups of 10 animals were given tralomethrin by gavage at 0, 500 (TOCP positive control), 1,500, 3,000, or 6,000 mg/kg. In this group, one hen in the control group died. Three animals in the positive control group were killed due to severe signs of ataxia. Four animals died in the high dose group (6,000 mg/kg). Two animals in the high dose group exhibited signs of unsteadiness on their legs for several days after dosing. Both animals recovered by day 5 of the study. Due to the reported recovery, the signs were not considered to be associated with delayed neurotoxicity. No repeat dosing after 21 days was conducted as required in the absence of neurotoxicity in the first period of 21 days. DPR considered the study incomplete and unacceptable as a FIFRA guideline study. Since, however, there is not FIFRA requirement for a delayed neurotoxicity study for pyrethroid-type pesticides, there is not a neurotoxicity "data-gap" for tralomethrin.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

1. Acute Toxicity

As indicated in the toxicology profile section of this document, laboratory animal studies have demonstrated toxicity in response to acute exposure to tralomethrin. In studies specifically designed to evaluate the toxicity of acute exposure to tralomethrin, the primary toxic signs are characteristic of cholinergic toxicity. This is consistent with the neurotoxicity associated with synthetic pyrethroids. Specific clinical signs reported in acute toxicity (LD_{50}) studies included: ptosis, labored respiration, locomotion difficulties, sedation, convulsions, tremors, and death. Furthermore, toxicologically significant effects (liquid feces, vomiting, tremors, and death) attributed to acute toxicity have been reported in animals undergoing multiple exposure to tralomethrin (Chesterman, et al., 1978). In a sub-chronic toxicity study (Chesterman, 1978), dogs exhibited a dose-related increase in the incidence of diarrhea (liquid feces) at doses of 0.1 mg/kg/day and greater. This response occurred within hours after dosing during the first week of the study, therefore, was considered the result of acute exposure. At doses greater than 0.1 mg/kg/day, the reported effects included vomiting (1 and 10 mg/kg/day) and tremors (10 mg/kg/day). Liquid feces, vomiting, and tremors are classic signs of autonomic nervous system dysfunction.

On the basis of the dose-related increase in autonomic nervous system dysfunction (diarrhea/liquid feces), an acute **LOEL of 0.1 mg/kg/day** was established for tralomethrin. An estimated NOEL of **0.01 mg/kg/day** was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10 (U.S. EPA, 1987c). This value will be used in calculating margins of safety for acute exposure to tralomethrin.

2. Sub-Chronic Toxicity

Sub-chronic toxicology studies are generally used as preliminary studies for establishing dose levels for chronic studies. They usually involve exposure to a substance for a period spanning approximately 10% of an organism's lifetime. For this risk assessment, sub-chronic toxicity is defined as a toxic response associated with repeated exposures to tralomethrin. The repeated exposures must be over a duration of at least one week but significantly less than annual or lifetime exposures. The sub-chronic toxicity assessment is intended to assist in determining potential risk to agricultural workers involved with seasonal exposure to tralomethrin. Potential adverse effects have been associated with sub–chronic exposure to tralomethrin in a number of studies (see Toxicology Profile section of this document).

A 90-day oral toxicity study with CD rats established a NOEL of 1 mg/kg/day. This was based on mortality observed at dosages of 6 mg/kg/day or greater. In CD-1 mice, a NOEL of 10 mg/kg/day was established on the bases of deaths, clonic convulsions, and unsteady gait reported at dosages of 15 mg/kg/day or greater. In the dog study, a sub-chronic LOEL of 0.1 mg/kg/day was established on the basis of exaggerated patellar reflexes, liquid feces and vomiting.

On the basis of the exaggerated patellar reflexes, vomiting, and liquid feces, the LOEL for sub-chronic exposure to tralomethrin was 0.1 mg/kg/day. An estimated sub-chronic NOEL of **0.01 mg/kg/day** was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10 (U.S. EPA, 1987c). This value will be used in calculating margins of safety for sub-chronic (i.e., seasonal) exposure to tralomethrin.

3. Chronic Toxicity

The toxicity potential for chronic tralomethrin exposure has been established in mice, rats, and dogs (see Toxicology Profile section) On the basis of dermatitis reported at oral doses of 0.75 mg/kg/day and greater in mice, the LOEL established in this risk assessment was 0.75 mg/kg/day (Spicer, 1980). An estimated chronic NOEL of **0.075 mg/kg/day** was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10 (U.S. EPA, 1987c). This value will be used in calculating margins of safety for chronic exposure to tralomethrin.

4. Oncogenicity

On the basis of the data reviewed (Spicer, 1983a and 1984), no evidence of oncogenicity potential has been associated with tralomethrin exposure.

5. Other Toxicity

Genotoxicity

Tralomethrin was tested for genotoxic potential both *in vitro* and *in vivo*. Assays included the *Salmonella* gene mutation assay (Ames test), the host mediated assay, the L5178Y mouse lymphoma assay, tests for *in vitro* and *in vivo* chromosomal aberrations, a mouse dominant lethal assay, tests for DNA damage, and tests for morphological cell transformation. Genotoxic potential was indicated in the L5178Y mouse lymphoma assay in the presence of metabolic activation. In all other systems examined, no genotoxic potential was reported.

Reproductive and Developmental Toxicity
While no chemically related "reproductive effects" were reported in the reproductive studies evaluated, developmental effects were noted (Spicer, 1983b). A developmental NOEL of 3 mg/kg/day was established on the basis of decreased pup weight and increased neonatal mortality at 12 mg/kg/day. A NOEL of 0.75 mg/kg/day was established for weanlings on the basis of convulsions and death at 3 mg/kg/day.

In a study designed to evaluate the developmental effects of tralomethrin in New Zealand White rabbits, abortions were reported, at 25 mg/kg/day (Schardein, 1989). On the basis of this adverse effect, the developmental toxicity was established at 12.5 mg/kg/day.

B. EXPOSURE ASSESSMENT

1. Occupational Exposure

Occupational exposure to tralomethrin has been evaluated by the Worker Health and Safety branch of DPR (Thongsinthusak, 1995). Tralomethrin uses included treatment of cotton (Scout X-TRA™), professional pest control (SAGA®WP), and ready-to-use, do-it-your-self pest control (Hot Shot® and Spectracide® products). TABLE XI presents dosage estimates, in μg/kg/day, for single day (absorbed daily dosage, ADD), seasonal (seasonal average dosage, SADD), annual (annual average daily dosage, AADD) and lifetime (lifetime average daily dosage, LADD) exposures to agriculture workers involved in the treatment of cotton. The acute absorbed-daily-dosage is presented as a mean (ADD) and upper bound (either the maximum based on the range, or the mean ± two standard deviations) exposure (ADD*) estimate, while the daily dosage estimates for seasonal, annual, and lifetime exposures are presented only as mean values. This risk assessment assumes that an individual is unlikely to receive the maximum single day exposure every day of a multiple exposure scenario (i.e., seasonal, annual, lifetime exposures). As indicated in TABLE XI, mixer/loaders involved in the aerial application of tralomethrin to cotton have the highest calculated dosages.

TABLE XI: Tralomethrin: Estimated average daily dosages (daily, seasonal, annual, and lifetime) for agricultural workers involved in the treatment of cotton[a].

	Dosage (µg/kg/day)				
Worker	**ADD**	**ADD***	**SADD**	**AADD**	**LADD**
Aerial Application[b]					
Mixer/Loader	0.820	2.120	0.670	0.11	0.060
Applicator	0.490	1.790	0.400	0.07	0.040
Flagger	0.180	0.530	0.140	0.02	0.013
Ground Boom Application[c]					
Mixer/Loader	0.020	0.040	0.006	0.001	0.001
Applicator	0.060	0.440	0.019	0.003	0.002
Mixer/Loader/Applicator	0.080	0.480	0.025	0.004	0.003
Cotton Scout[d]					
Gloved	0.270	0.550	0.180	0.03	0.020
Not Gloved	0.480	0.960	0.310	0.05	0.030

a The following factors were used in the estimation of exposures: adult male body weight = 75.9 kg, dermal absorption rate = 7.2%, inhalation uptake/absorption = 50%, years of employment = 40, life expectancy = 75 years (Thongsinthusak, 1995).
b Assumed 50 workdays in a 62-day season.
c Assumed 20 workdays in a 62-day season.
d Assumed 40 workdays in a 62-day season.
ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

For the purposes of this risk assessment, occupational exposure has been defined as exposures relating to agricultural, professional pest control, and residential use. TABLE XII presents ADD, AADD, and LADD dosage estimates for pest control operators (PCOs) and do-it-your-self home applicators and infants exposed due to residential use. As indicated in TABLE XII, the individuals with the highest estimated dosage following acute exposure were infants who were exposed following tralomethrin application by pest control operators. For annual and lifetime exposures, the individuals with the highest expected dosage were pest control operator mixer/loader/applicators.

TABLE XII: Tralomethrin: Estimated average daily dosages (daily, seasonal, annual, and lifetime) for pest control operators (PCOs), and do-it-your-self home applicators, and infants exposed due to residential use[a].

	Dosage (μg/kg/day)			
	ADD	**SADD**	**AADD**	**LADD**
Broadcast Application				
Residential PCO (M/L/A)[b]	1.570	1.710	0.23	0.120
Infants[c]	3.040	6.020	0.06	N/A
Adults[d]	1.580	3.360	0.03	0.020
Home Application				
Infants[e]	0.380	0.940	0.016	N/A
Home Applicators[f]	0.030	0.850	0.0003	0.0001

a The following factors were used in the estimation of exposures: adult male body weight = 75.9 kg, infant body weight = 12.2 kg, dermal absorption rate = 7.2%, inhalation uptake/absorption = 50%, years of employment = 40, life expectancy = 75 years (Thongsinthusak, 1995).
b The assumed number of workdays per year was 223.
c The assumed number of days exposed per year was 15 (3 applications/year x 5 days/application). Infants were assumed to be wearing diapers.
d The assumed number of days exposed per year was 15 (3 applications/year x 5 days/application). Adults were assumed to be wearing "minimal clothing.
e The assumed number of days exposed per year for infants was 15.
f The assumed number of days exposed per year for adults was 3.
ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., upper limit of range for PCO mixer/loader/applicators, mean + 2SD for all others.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.
N/A Not applicable.
PCO Pest control operator.
M/L/A Mixer/Loader/Applicator.

2. Dietary Exposure

DPR evaluates the risk of exposure to an active ingredient in the diet using two processes: (1) use of residue levels detected in foods to evaluate the risk from total exposure, and (2) use of tolerance levels to evaluate the risk from exposure to individual commodities (see the Tolerance Assessment of this document). For the evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities, processed forms, and animal products (meat and milk) that have established U.S. EPA tolerances. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

a) Residue Data

The sources of residue data for dietary exposure assessment include DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group as defined by U.S. EPA or theoretical residues equal to U.S. EPA tolerances are used. Residue levels that exceed established tolerances (over-tolerance) are not utilized in the dietary exposure assessment because over-tolerance incidents are investigated by the DPR Pesticide Enforcement Branch and are relatively infrequent. DPR evaluates the potential risk from consuming commodities with residues over tolerance levels using an expedited acute risk assessment process.

DPR has four major sampling programs: (1) priority pesticide, (2) preharvest monitoring, (3) produce destined for processing, and (4) marketplace surveillance. The priority pesticide program focuses on pesticides of health concern as determined by DPR Enforcement and Medical Toxicology Branches. Samples are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both priority pesticide and marketplace surveillance are similar and are weighted toward such factors as pattern of pesticide use; relative number and volume of pesticides typically used to produce a commodity; relative dietary importance of the commodity; past monitoring results; and extent of local pesticide use. The preharvest monitoring program routinely examines the levels of pesticides on raw agricultural commodities in the field at any time during the growth cycle. Generally, these data are not used unless the application schedule is known and residue data are not available from other monitoring programs. Commodities destined for processing are collected in the field no more than 3 days prior to harvest, at harvest, or post-harvest before processing.

The United States Food and Drug Administration (FDA) has three monitoring programs for determining residues in food: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. For regulatory monitoring, surveillance samples are collected from individual lots of domestic and imported foods at the source of production or at the wholesale level. In contrast to the regulatory monitoring program, the total diet study monitors residue levels in the form that a commodity is commonly eaten or found in a prepared meal. The incidence/level monitoring program is designed to address specific concerns about pesticide residues in particular foods.

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level. The pesticide and produce combinations are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. In addition, USDA is responsible for the National Residue Program which provides data for potential pesticide residues in meat and poultry. These residues in farm animals can occur from direct application, or consumption of commodities or by-products in their feed.

TABLE XIII: Summary of tralomethrin residue values in cottonseed oil, cottonseed mill, and soybeans.

Commodity	Residue (ppm) Acute	Residue (ppm) Chronic	Data Source[a]
Cottonseed Oil	0.068	0.065	Registrant MDLs[a]
Cottonseed Meal	0.020	0.010	Registrant residues
Soybean	0.020	0.010	Registrant MDLs[j]
Soybean Oil	0.050	0.050	Registrant MDLs[j]

[a] Registrant supplied field residue data reported in Carr, 1995.

b) Acute Exposure

Estimates of potential acute (daily) dietary exposure use the highest measured residue values at or below the tolerance for each commodity. The following assumptions were used to estimate potential acute dietary exposure from measured residues: 1) the residue does not change over time, 2) the concentration of residue does not decrease when the raw agricultural commodity (RAC) is washed, 3) processing of RACs into various food forms does not reduce the residue, and 4) all foods that are consumed will contain the highest reported residue.

Acute dietary exposure analyses were conducted using the Exposure-4™ computer program developed by Technical Assessment Systems, Inc. (TAS, 1992a). This software estimates the distribution of single-day exposures for the overall U.S. population and specific population sub-groups. The analysis utilizes food consumption data, as reported by the U.S. Department of Agriculture (USDA, 1988). Exposure-4™ is designed to evaluate exposure to chemical residues as a function of consumer-days. A consumer-day is any day in which at least one commodity is consumed.

On the basis of the 95th percentile of user-day exposures, the potential acute dietary exposure of tralomethrin, from cotton and soybean products, to the U.S. population was approximately 0.06 μg/kg/day (TABLE XIV). Potential acute exposures for the population subgroups examined ranged from 0.04 to 0.14 μ g/kg/day. The population subgroup with the highest estimated dosage (0.25 μ g/kg/day) was non-nursing infants less than 1 year of age. The estimated dosage assumed for potential workers was approximately 0.04 μg/kg/day (U.S. Population ages 16 and greater).

TABLE XIV: Potential acute dietary exposure to tralomethrin from residues in cotton and soybeans.

Population Sub-group	Dosage (μg/kg body wt/day)[a,b]
U.S. Population	0.056
Western Region - U.S. Population	0.053
Nursing Infants (<1 year)	0.140
Non-Nursing Infants (<1 year)	0.251
Females (13+/P[c]/NN[d])	0.036
Females (13+N[e])	0.039
Children (1-6 years)	0.105
Children (7-12 years)	0.073
Males (13-19 years)	0.051
Females (13-19 years/NP[f]/NN)	0.046
Males (20+ years)	0.043
Females (20+/NP/NN)	0.039
Seniors (55+ years)	0.039
U.S. Population (16+ years)	0.041

a = Exposure is evaluated as a function of user-days (i.e., day which at least one commodity containing tralomethrin is consumed).
b = Values represent the 95th percentile of consumer-day exposure.
c = pregnant
d = not nursing
e = nursing
f = not pregnant

c) Chronic Exposure

Estimates of potential dietary exposure used the average of measured and "below detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the minimum detection limit (MDL) for each commodity. The following assumptions were used to estimate potential chronic dietary exposure from measured residues:

1) the residue level does not change over time, 2) residues are not reduced by washing the raw agricultural commodity (RAC), 3) processing of is assumed to be a t a level equivalent to the RAC residue level that may be multiplied by an adjustment factor, and 4) exposures to a commodity at all reported residue levels do occur, i.e., a commodity with the average calculated residue is consumed every day at an annual average level (dosage).

The potential chronic dietary exposure was calculated using the Exposure-1™ computer program developed by TAS (Technical Assessment Systems, Inc., 1992b). The food consumption data for the chronic analysis was also based on the 1987-88 United States Department of Agriculture Nationwide Food Consumption Survey (USDA, 1988). The program estimates the annual average exposure for all members of a designated population subgroup.

The calculated dosages following chronic dietary exposure to tralomethrin from cotton and soybean products, to the U.S. population, was approximately 0.02 μ g/kg/day (TABLE XV). Calculated dosages for the population subgroups examined ranged from approximately 0.01 to 0.09 μg/kg/day. The population subgroup with the highest estimated dosage was non-nursing infants less than 1 year of age. The estimated dosage assumed for potential workers was approximately 0.016 μ g/kg/day (highest dosage estimate for males and females aged 20 years and older).

TABLE XV: Potential chronic dietary exposure to tralomethrin from residues in cotton and soybeans.

Population Sub-group	Dosage (µg/kg body wt/day)[a]
U.S. Population	0.020
Western Region - U.S. Population	0.018
Nursing Infants (<1 year)	0.020
Non-Nursing Infants (<1 year)	0.091
Females (13+/P[b]/NN[c])	0.014
Females (13+N[d])	0.016
Children (1-6 years)	0.037
Children (7-12 years)	0.029
Males (13-19 years)	0.021
Females (13-19 years/NP[e]/NN)	0.018
Males (20+ years)	0.016
Females (20+/NP/NN)	0.014

a = Exposure estimates were based on daily consumption averaged over 365 days.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

3. Combined Exposure (Occupational and Dietary)

In an effort to predict total exposure to agricultural workers using tralomethrin, a combined exposure estimate was calculated by adding the estimated occupational and dietary exposures. The estimates for agricultural uses are shown in TABLE XVI. Estimates have been calculated for ADD (absorbed daily dosage), SADD (seasonal average daily dosage), AADD (annual average daily dosage), and LADD (lifetime average daily dosage). The occupational component of these exposure was presented in TABLE XI. For the ADD (acute exposure), the dietary component of exposure (0.041 µg/kg/day) was based on the 95th percentile of acute exposure for the United States population age 16 and above (TABLE XIV). For the SADD, AADD, and the LADD, the dietary component was 0.016 µg/kg/day and was based on the average daily dosage, to males 20 years and older (TABLE XIV).

TABLE XVI: Tralomethrin: Estimated average daily dosages (daily, seasonal, annual, and lifetime) for agricultural workers involved in the treatment of cotton. Dosage includes potential dietary exposure from cottonseed and soybean residues

	Dosage (µg/kg/day)				
Worker	**ADD**	**ADD***	**SADD**	**AADD**	**LADD**
Diet Contribution:	0.041	0.041	0.016	0.016	0.016
Aerial Application					
Mixer/Loader:	0.861	2.161	0.686	0.126	0.076
Applicator	0.531	1.831	0.416	0.086	0.056
Flagger	0.221	0.571	0.156	0.036	0.029
Ground Boom Application					
Mixer/Loader:	0.061	0.081	0.022	0.017	0.017
Applicator	0.101	0.481	0.035	0.019	0.018
Mixer/Loader/Applicator	0.121	0.521	0.041	0.020	0.019
Cotton Scout					
Gloved	0.311	0.601	0.196	0.046	0.036
Not Gloved	0.521	1.011	0.326	0.066	0.046

ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

TABLE XVII presents ADD, AADD, and LADD dosage estimates for pest control operators (PCOs), residents, and do-it-your-self home applicators. The non-dietary component of the exposures was presented in TABLE XII. For the ADD (acute exposure), the dietary component of exposure (0.041 µg/kg/day) was based on the 95th percentile of acute exposure for the United States population age 16 and above (TABLE XIV). For infants (ADD), the dietary component was 0.251 µ g/kg/day (TABLE XIV). For the SADD, AADD, and the LADD, the dietary component was 0.016 µg/kg/day and was based on the average daily dosage, to males 20 years and older (TABLE XIV). For infants (AADD only), the dietary component was 0.009 µg/kg/day (TABLE XIV).

TABLE XVII: Tralomethrin: Estimated average daily dosages (daily, seasonal, annual, and lifetime) for pest control operators (PCOs), residents, and do-it-your-self home applicators. Dosage includes dietary exposure.

	Dosage (μg/kg/day)			
Worker	**ADD**	**ADD***	**AADD**	**LADD**
Diet Contribution:	0.041	0.041	0.016	0.016
Broadcast Application				
Residential PCO (M/L/A)	1.611	1.751	0.246	0.136
Infants	3.291	6.271	0.150	N/A
Adults	1.621	3.401	0.046	0.036
Home Application				
Infants	0.631	1.191	0.106	N/A
Home Applicators	0.071	0.891	0.016	0.016

ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.
PCO Pest control operator.
M/L/A Mixer/Loader/Applicator.

a) Acute Exposure

As indicated, in TABLEs XVI and XVII, individuals with the highest expected dosage following acute exposure were infants who were exposed following tralomethrin application by pest control operators. The calculated maximum potential dosage for this group of individuals was approximately 6.3 μg/kg/day.

b) Seasonal Exposure

For seasonal exposures, calculated dosages ranged from less than 0.02 μg/kg/day to approximately 0.7 μg/kg/day. The individuals with the highest expected dosage were mixer/loaders involved in the aerial application of tralomethrin to cotton.

c) Annual Exposure

For annual exposures, calculated dosages ranged from less than 0.02 µg/kg/day to approximately 0.2 µg/kg/day. The individuals with the highest expected dosage were residential pest control operators (mixer/loader/applicators).

d) Lifetime Exposure

For lifetime exposures, calculated dosages ranged from léss than 0.02 µg/kg/day to approximately 0.1 µg/kg/day. The individuals with the highest expected dosage were residential pest control operators (mixer/loader/applicators).

C. RISK CHARACTERIZATION

In order to characterize the potential risks associated with exposure to tralomethrin, margins of safety (MOSs) were calculated for exposures resulting from occupational use and/or consumption of commodities with tralomethrin residues (i.e., dietary exposure). An MOS is defined as the ratio of the No-Observed-Effect-Level (NOEL) to the absorbed dosage. Experimentally determined NOELs were described in the Toxicology Profile and Hazard Identification sections of this document. Estimates of absorbed dosages were determined by the Worker Health and Safety Branch of DPR (Thongsinthusak, 1995) and presented in the Exposure Section. In general, a margin of safety equal to or greater than 10 is considered protective of human health when it is based on NOELs from human studies. When exposure is based on NOELs from non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100). Margins of safety for exposure to tralomethrin were all based on NOELs from laboratory animal data.

1. Occupational Exposure

In TABLEs XVIII and XIX, margins of safety are presented for tralomethrin exposures related to agricultural, professional pest control, residential use (exclusive of dietary exposure). This risk assessment assumes that it is unlikely that an individual will be exposed to maximum or upper bound potential daily exposures over a repeated exposure scenario. Margins of safety for seasonal, annual, and lifetime were, therefore, based on average dosage estimates.

TABLE XVIII: Tralomethrin: Margins of safety based on estimated average daily dosages (daily, seasonal, annual, and lifetime) for agricultural workers involved in the treatment of cotton. Dosages used in the calculation did not include dietary exposures[a].

	Margin of Safety			
Worker	**ADD[b]**	**ADD*[b]**	**SADD[c]**	**AADD[d]**
NOEL:	0.01	0.01	0.01	0.075
Aerial Application				
Mixer/Loader:	12	5	15	680
Applicator	20	6	25	1100
Flagger	56	19	71	3800
Ground Boom Application				
Mixer/Loader:	500	250	1700	75000
Applicator	167	23	530	25000
Mixer/Loader/Applicator	125	21	400	19000
Cotton Scout				
Gloved	37	18	56	2500
Not Gloved	21	10	32	1500

a Margin of Safety defined as the no observed effect level (NOEL) divided by the estimated dosage. Dosages were presented in the Exposure section. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.
b The NOEL was based on autonomic dysfunction (diarrhea/liquid feces).
c The NOEL was based on autonomic dysfunction (exaggerated patellar reflexes, vomiting, and diarrhea/liquid feces).
d The NOEL was based on dermatitis.
ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

TABLE XIX: Tralomethrin: Margins of safety based on estimated average daily dosages (daily, annual, and lifetime) for pest control operators (PCOs), residents, and do-it-your-self home applicators. Dosages used in calculations did not include dietary exposures.[a]

	Margin of Safety		
Worker	**ADD**[b]	**ADD***[b]	**AADD**[c]
NOEL:	0.01	0.01	0.075
Broadcast Application			
Residential PCO (M/L/A)r	6	6	330
Infants	3	2	1300
Adults	6	3	2500
Home Application			
Infants	26	11	4700
Home Applicators	330	12	75000

a Margin of Safety defined as the no observed effect level (NOEL) divided by the estimated dosage. Dosages were presented in TABLEs XI and XII. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number, all other values have been rounded to two significant digits.
b The NOEL was based on autonomic dysfunction (diarrhea/liquid feces).
c The NOEL was based on dermatitis.
ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
AADD Annual Average Daily Dosage based on mean exposure.
PCO Pest control operator.
M/L/A Mixer/Loader/Applicator.

a) Acute Exposure

As indicated in TABLEs XVIII and XIX, estimated margins of safety based on average acute exposure estimates and NOELs based on autonomic dysfunction (diarrhea/liquid feces), were greater than 100 for activities involved in ground boom application, and home applicators. All other activities had margins of safety less than 100. When tralomethrin exposure was based on the estimated upper bound (mean ± 2SD, or maximum value from range), all margins of safety were less than 100, with the exception of mixer/loaders involved in the ground boom application of the pesticide.

b) Seasonal Exposure

Calculated margins of safety based on seasonal exposures were less than 100 for mixer/loaders, applicators, and flaggers involved in the aerial application of tralomethrin to cotton, as well as, to cotton scouts. All activities related to ground boom application to cotton were greater than 100.

Seasonal exposure does not apply to residential PCO or home applications (i.e., margins of safety were not calculated for these activities.

c) Annual Exposure

On the basis of annual exposure estimates, calculated margins of safety for all agricultural and residential activities were greater than 100

d) Life-time Exposure

All life-time daily exposure estimates were equal to or less than annual exposure estimates. Since the NOEL for these exposure scenarios is the same, and since margins of safety for all activities from tralomethrin use were greater than 100 for annual exposures, margins of safety for activities related to life-time exposures were also greater than 100.

2. Dietary Exposure

a) acute (daily) exposure

Margins of safety for potential acute dietary exposure to tralomethrin were calculated by taking the ratio of the experimentally determined NOEL to the potential dietary dosage (the NOEL used was 0.01 mg/kg/day based autonomic dysfunction (diarrhea/liquid feces). The values presented in TABLE XX reflect the potential dietary exposure from cotton and soybean products. As indicated, margins of safety are less than 100 for infants and children ages 1 to 6. For all other population sub-groups, margins of safety are greater than 100.

TABLE XX: Tralomethrin: Calculated margins of safety (MOS) based on potential acute dietary exposure from residues in cotton and soybean products.

Population Sub-group	MOS[a]
U.S. Population	180
Western Region - U.S. Population	190
Nursing Infants (<1 year)	71
Non-Nursing Infants (<1 year)	40
Females (13+/P[b]/NN[c])	280
Females (13+N[d])	260
Children (1-6 years)	95
Children (7-12 years)	140
Males (13-19 years)	200
Females (13-19 years/NP[e]/NN)	220
Males (20+ years)	230
Females (20+/NP/NN)	260
Seniors (55+ years)	260
U.S. Population (16+ years)	240

a = Margin of safety defined as the NOEL divided by the estimated dosage. The NOEL used for acute exposure was 0.01 mg/kg based on autonomic nervous system dysfunction (diarrhea/liquid feces) effects in dogs. All values have been rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

b) Chronic Exposure

Margins of safety for annual dietary exposures were based on an estimated NOEL of 0.075 mg/kg/day (dermatitis). As indicated in TABLE XXI, all values are greater than 100.

TABLE XXI: Tralomethrin: Calculated margins of safety (MOS) based on potential chronic dietary exposure from residues in cotton and soybean products.

Population Sub-group	MOS[a]
U.S. Population	500
Western Region - U.S. Population	560
Nursing Infants (<1 year)	500
Non-Nursing Infants (<1 year)	110
Females (13+/P[b]/NN[c])	710
Females (13+N[d])	630
Children (1-6 years)	270
Children (7-12 years)	350
Males (13-19 years)	480
Females (13-19 years/NP[e]/NN)	560
Males (20+ years)	630
Females (20+/NP/NN)	710

a = Margin of safety defined as the NOEL divided by the estimated dosage. The NOEL used for acute exposure was 0.075 mg/kg/day based on a systemic in dermatitis in mice. All values have bee rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

3. Combined (Occupational and Dietary) Exposure

In TABLEs XXII and XXIII, margins of safety are presented for tralomethrin exposures related to agricultural, professional pest control, and residential use (including dietary exposure). This risk assessment assumes that it is unlikely that an individual will be exposed to maximum potential daily exposures over a multiple exposure scenario. Margins of safety for seasonal, annual, and lifetime exposures were, therefore, based on average dosage estimates.

TABLE XXII: Tralomethrin: Margins of safety based on estimated daily, seasonal, annual, and lifetime dosages for agricultural workers involved in the treatment of cotton. Dosages used in the calculation did include dietary exposures.[a]

	Margin of Safety			
Worker	**ADD[b]**	**ADD*[b]**	**SADD[c]**	**AADD[d]**
NOEL:	0.01	0.01	0.01	0.075
Aerial Application				
Mixer/Loader	12	5	15	600
Applicator	19	5	24	870
Flagger	45	18	64	2100
Ground Boom Application				
Mixer/Loader	164	123	460	4400
Applicator	99	21	290	3900
Mixer/Loader/Applicator	83	19	240	3800
Cotton Scout				
Gloved	32	17	51	1600
Not Gloved	19	10	31	1100

a Margin of Safety defined as the no observed effect level (NOEL) divided by the estimated dosage. Dosages were presented in the Exposure section. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.
b The NOEL was based on autonomic dysfunction (diarrhea/liquid feces).
c The NOEL was based on autonomic dysfunction (exaggerated patellar reflexes, vomiting, and diarrhea/liquid feces).
d The NOEL was based on dermatitis.
ADD Absorbed Daily Dosage based on mean exposure.
ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

TABLE XXIII: Tralomethrin: Margins of safety based on estimated daily, annual, and lifetime dosages for pest control operators (PCOs), residents, and do-it-yourself home applicators. Dosages used in calculations did include dietary exposures.[a]

	Margin of Safety		
Worker	**ADD[b]**	**ADD*[b]**	**AADD[c]**
NOEL:	0.01	0.01	0.075
Broadcast Application			
Residential PCO (M/L/A)	6	6	300
Infants	3	2	500
Adults	6	3	1600
Home Application			
Infants	16	8	710
Home Applicators	141	11	4600

a Margin of Safety defined as the no observed effect level (NOEL) divided by the estimated dosage. Dosages were presented in TABLEs XI and XII. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number, all other values have been rounded to two significant digits.

b The NOEL was based on autonomic dysfunction (diarrhea/liquid feces).

c The NOEL was based on dermatitis.

ADD Absorbed Daily Dosage based on mean exposure.

ADD* Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.

AADD Annual Average Daily Dosage based on mean exposure.

PCO Pest control operator.

M/L/A Mixer/Loader/Applicator.

a) Acute Exposure

As indicated in TABLEs XXII and XXIII, estimated margins of safety based on average acute exposure estimates and NOELs based on autonomic dysfunction (diarrhea), were greater than 100 for mixer/loaders (applicators, 99) involved in ground boom application, and home applicators. All other activities had margins of safety less than 100. When tralomethrin exposure was based on the estimated upper bound (mean ± 2SD, or maximum value from range), all margins of safety were less than 100, with the exception of mixer/loaders involved in the ground boom application of the pesticide.

b) Seasonal Exposure

Calculated margins of safety based on seasonal exposures were less than 100 for mixer/loaders, applicators, and flaggers involved in the aerial application of tralomethrin to cotton, as well as, to cotton scouts. All other activities had margins of safety greater than 100.

Seasonal exposure does not apply to residential PCO or home applications (i.e., margins of safety from combined dietary/residential use were not calculated.

c) Annual Exposure

On the basis of annual exposure estimates, calculated margins of safety for all use related activities were greater than 100

d) Life-time Exposure

All life-time daily exposure estimates were equal to or less than annual exposure estimates. Since the NOEL for these exposure scenarios is the same, and since margins of safety for all activities from tralomethrin use were greater than 100 for annual exposures, margins of safety for activities related to life-time exposures were also greater than 100.

V. RISK APPRAISAL

A health risk assessment was conducted for the potential exposure of tralomethrin to agricultural workers, pest control operators, those who come in contact due to home use, and the general public from dietary sources (cotton and soybean products). The routes of exposure considered were dermal, inhalation, oral. For agricultural use, acute, seasonal, annual, and life-time exposure conditions were considered. For PCOs and home applications, acute, annual exposures were considered. For dietary exposure, acute and chronic (annual) exposure scenarios were considered.

Risk assessment is the process used to evaluate the potential for human exposure to a substance and the likelihood that the potential exposure will cause adverse health effects in humans under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to the prediction of potential risk to the human population. This makes it necessary for certain assumptions and extrapolations to be incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in a level of uncertainty in the risk characterization. Qualitatively, risk assessments for all chemicals have similar uncertainties. The degree or magnitude of the uncertainty, however, can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. One of the primary assumptions, which is inherent in all risk assessments using animal data, is that effects observed in laboratory animals represent expected effects in humans at comparable dosages. It not known if this assumption over or under estimates the potential risk. In the absence of actual human data, however, this assumption and the resulting extrapolation are necessary. Other areas of uncertainty specific to this risk assessment are delineated in the following discussion.

As indicated in the toxicology profile section of this manuscript, the primary effects associated with tralomethrin exposure includes excessive salivation, vomiting, diarrhea/liquid feces, uncoordinated body movements, tremors, and convulsions. All of these signs are classic indicators of autonomic nervous system dysfunction. Furthermore, most of these signs appear in various species when exposed to tralomethrin. For example: excessive salivation occurs in rats, mice, and dogs; diarrhea/liquid feces occurs in rats, dogs, and rabbits; uncoordinated movements occurs in rats, mice, dogs, rabbits, and hens; tremors and or convulsions occurs in mice and dogs. On the basis of the reported spectrum of effects (primarily autonomic nervous system dysfunction, this risk assessment assumes that the effects can occur in humans. This is confirmed by the reported signs of autonomic nervous system dysfunction (vomiting and tremors) in humans following exposure to deltamethrin (the primary metabolite of tralomethrin).

For occupational exposure, a number of assumptions and extrapolations were necessary. In some cases, actual exposure data from tralomethrin use did not exist. Surrogate exposure studies were, therefore, used to predict actual potential exposures (see Thongsinthusak , 1995 for complete discussion). In each case, however, the values used were considered the best available information. As expected, uncertainties are inherent whenever extrapolations from surrogate data are used. While the intent in this risk assessment has been to err on the side of protecting public health, it is not know for certain if the extrapolations made in the occupational exposure resulted in over or under estimates of potential exposures.

In addition to the dermal and inhalation routes from exposure, dietary exposure was evaluated in order to estimate a combined potential exposure for the various activities.

The dietary component was based on a national consumption survey conducted by the U.S. Department of Agriculture. The exposure data used in the acute dietary assessment of workers was restricted to those survey respondents age 16 years and older. For seasonal, annual, and lifetime exposures, the dietary component was based on the average daily dosage to males over the age of 19. These values assume that the number of workers under these ages are too small to influence the interpretation of the analysis. Furthermore, inherent in the use of the national survey is the assumption that the result is representative of California residents.

In the dietary assessment, since neither table top nor market basket data were available, residue estimates were based on field trials and tolerance values. These field studies were conducted to establish tolerances for specific raw agricultural commodities and, therefore, were designed to obtain the highest potential residue under the conditions indicated on the product label. When field study data were inadequate or non-existent, residue values were assumed at tolerance levels. The resulting estimate of exposure was likely an overestimate of actual exposure from dietary sources. Furthermore, it was assumed that residue levels were stable; i.e., residue values do not change over time, the concentration does not decrease when the commodity is washed, the residue concentration is not reduced by processing of the commodity, and all consumed commodities contain the highest reported residue.

In general, a margin of safety equal to or greater than 10 is considered protective of human health when it is based on NOELs from human studies. When exposure is based on NOELs from non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100). For tralomethrin margins of safety were based on animal data.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

A tolerance is the maximum, legal amount of a pesticide residue that is allowed on a raw or processed agricultural commodity, or in an animal tissue used for human consumption. The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g., improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to non-approved commodities). Tolerances are enforced by the food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies (e.g., Pesticide Enforcement Branch of DPR).

Current pesticide tolerances are generally set at levels that are not expected to produce deleterious health effects in humans from chronic dietary exposure. The data requirements for establishing a specific tolerance include: 1) toxicology data for the parent compound, major metabolites, degradation products and impurities, 2) product chemistry, 3) analytical methods(s) that are readily available, accurate and precise, 4) measured residues in crops used for animal feeds, 5) measured residues in animal tissues (e.g., meat, milk, and eggs) from direct or indirect (feed) applications, 6) measured residue levels from field studies. The minimum requirements for the field study include: 1) an application rate at or above the highest rate on the product label, 2) the greatest number of allowable repeat applications, 3) the shortest pre harvest interval listed on the product label. Generally, the registrant of the pesticide requests a commodity-specific tolerance, which is equal to the highest measured residue, or some multiple of that value, from the field trial using the specific pesticide.

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides." In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance" As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population sub-groups can be calculated from the product of the tolerance and the daily consumption rate.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4™ software program and the USDA consumption data base are used in the assessment. The acute tolerance assessment does not routinely address multiple commodities at tolerance levels since the probability of consuming multiple commodities at these levels decreases as the number of commodities included in the assessment increases.

A dietary exposure assessment for tralomethrin exposure was conducted using tolerance levels as assumed residue values. TABLE XXIV shows the calculated margin of safety (MOS) range for each label approved commodity.

TABLE XXIV: Tralomethrin tolerances and corresponding margins of safety (MOSs) following acute dietary exposure. (NOTE: MOSs are based on residues at tolerance levels)

Commodity	Tolerance (ppm)	Margins of Safety low	Margins of Safety high
Cottonseed	0.02	>1,000	>4,000
Soybeans	0.05	<100[a]	>300

[a] Non-Nursing and Nursing Infants less than 1 year of age

C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations or commodities has not been conducted because it is highly improbable, if not impossible, that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from CDFA pesticide monitoring programs that indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

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APPENDIX I Tralomethrin: Clinical signs reported from an 8-week oral toxicity study conducted in Charles River CD-1 mice (Laveglia, 1980b). Effects are reported for males (M) and females (F)

Percentage of Mice with Signs[1]

	Dosage Level (mg/kg/day)											
	0		5		10		15		20		30	
	M	F	M	F	M	F	M	F	M	F	M	F
Yellow Staining	20	0	20	0	60	30	100	100	90	70	70	50
Excessive Salivation	0	0	0	0	20	10	100	80	90	90	50	40
Clonic Convulsions	0	0	0	0	0	0	50	0	90	80	100	90
Unsteady Gate	0	0	0	0	10	0	90	70	70	90	0	0
Death	0	0	0	0	0	0	30	10	100	40	100	100

[1] Ten male and ten female animal per dose.

APPENDIX II Tralomethrin: Clinical signs reported in report of 13-week oral toxicity study conducted in beagles (Chesterman, et al., 1978). Effects are reported for males (M) and females (F)

Clinical Signs (Incidence)[1,2,3]

Signs	Dosage Level (mg/kg/day)							
	Control		0.1		1.0		10.0	
	M	F	M	F	M	F	M	F
Milk Suppliment Refusal								
Week 1	0	0	0	0	0	0	1	0
Weeks 2-5	0	0	0	0	8	0	8	36
Weeks 6-9	0	2	1	0	2	0	0	9
Weeks 10-13	0	1	0	0	7	2	0	2
Weeks 1-13	0	3	1	0	17	2	9	47
Vomiting								
Week 1	0	0	0	0	1	1	10	7
Weeks 2-5	0	1	0	2	0	2	4	4
Weeks 6-9	0	0	0	0	2	0	6	2
Weeks 10-13	0	0	0	0	2	1	4	3
Weeks 1-13	0	1	0	2	5	4	24	16
Liquid Feces								
Week 1	0	1	1	6	7	4	10	7
Weeks 2-5	5	1	12	12	20	16	114	30
Weeks 6-9	2	5	3	3	9	9	11	24
Weeks 10-13	2	1	10	4	12	6	12	14
Weeks 1-13	9	8	27	25	48	36	171	125
Tremors/Uncoordination								
Week 1	0	0	0	0	0	0	4	4
Weeks 2-5	0	0	0	0	0	0	31	112
Weeks 6-9	0	0	0	0	0	0	9	28
Weeks 10-13	0	0	0	0	0	0	5	12
Weeks 1-13	0	0	0	0	0	0	49	26

1 Clinical signs were not recorded after 5:30 pm during the work-week or after "mid-day" on weekends and holidays (Note exception in footnote 2).

2 Clinical signs were not recorded on days 3, 4, 5, and 6.

3 Five male and five female animals for each dose group

APPENDIX III Tralomethrin: Clinical signs reported in report of 1-year oral toxicity study conducted in beagles (Spicer, 1980).

	Clinical Signs (Incidences/Animals)[1,2] Dosage Level (mg/kg/day)							
Signs	**Control**		**0.75**		**3.0**		**10.0**	
Weeks	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Soft Stool/Diarrrhea								
1-13	8/8	8/8	8/8	8/8	8/8	8/8	8/8	8/8
14-26	8/8	8/8	8/8	8/8	8/8	8/8	8/8	7/7
27-39	4/6	5/6	6/6	6/6	6/6	6/6	6/6	5/5
40-52	6/6	4/6	6/6	6/6	6/6	5/6	6/6	5/5
Vomiting								
1-13	2/8	6/8	6/8	7/8	8/8	8/8	8/8	8/8
14-26	5/8	7/8	6/8	5/8	7/8	8/8	8/8	7/7
27-39	5/6	4/6	2/6	3/6	5/6	6/6	5/6	5/5
40-52	5/6	4/6	5/6	4/6	6/6	6/6	6/6	5/5
Ptyalism								
1-13	5/8	3/8	7/8	3/8	7/8	7/8	8/8	8/8
14-26	6/8	3/8	5/8	4/8	8/8	6/8	8/8	7/7
27-39	3/6	3/6	1/6	3/6	5/6	5/6	5/6	5/5
40-52	5/6	1/6	4/6	3/6	5/6	5/6	5/6	3/5
Tremors								
1-13	0/8	0/8	0/8	1/8	2/8	1/8	8/8	8/8
14-26	0/8	0/8	0/8	0/8	0/8	0/8	8/8	6/7
27-39	0/6	0/6	0/6	0/6	0/6	1/6	5/6	2/5
40-52	0/6	0/6	0/6	0/6	0/6	0/6	6/6	2/5
Convulsions								
1-13	0/8	0/8	0/8	1/8	0/8	0/8	6/8	4/8
14-26	0/8	0/8	0/8	0/8	0/8	0/8	0/8	2/7
27-39	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
40-52	0/6	0/6	0/6	0/6	0/6	0/6	1/6	0/5
Ataxia								
1-13	0/8	0/8	0/8	0/8	0/8	0/8	8/8	8/8
14-26	0/8	0/8	0/8	0/8	0/8	0/8	8/8	7/7
27-39	0/6	0/6	0/6	0/6	0/6	1/6	6/6	5/5
40-52	0/6	0/6	0/6	0/6	0/6	0/6	6/6	4/5
Irregular Heart Rhythm								
1-13	NR	NR	NR	NR	NR	NR	4/8	3/8
14-26	NR	NR	NR	NR	NR	NR	2/8	0/7
27-39	NR	NR	NR	NR	NR	NR	1/6	0/5
40-52	NR	NR	NR	NR	NR	NR	2/6	0/5
Death								
1-13	0/8	0/8	0/8	0/8	0/8	0/8	0/8	1/8
14-26	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
27-39	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
40-52	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6

1 Clinical signs were not recorded after 5:30 pm during the work-week or after "mid-day" on weekends and holidays (Note exception in footnote 2).
2 Clinical signs were not recorded on days 3, 4, 5, and 6.